Review Report

May 15, 2015
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	(a) Eylea Intravitreal Injection 40 mg/mL (b) Eylea Intravitreal Injection Kit 40 mg/mL
[Non-proprietary name]	Aflibercept (Genetical Recombination) (JAN*)
[Applicant]	Bayer Yakuhin, Ltd.
[Date of application]	August 28, 2014
[Dosage form/Strength]	(a) A solution for intravitreal injection containing 11.12 mg of Aflibercept (Genetical Recombination) per vial (0.278 mL) (b) A solution for intravitreal injection containing 6.6 mg of Aflibercept (Genetical Recombination) per syringe (0.165 mL)
[Application classification]	Prescription drug, (4) Drug with a new indication
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug III

**Japanese Accepted Name (modified INN)*

Review Results

May 15, 2015

[Brand name]	(a) Eylea Intravitreal Injection 40 mg/mL (b) Eylea Intravitreal Injection Kit 40 mg/mL
[Non-proprietary name]	Aflibercept (Genetical Recombination)
[Applicant]	Bayer Yakuhin, Ltd.
[Date of application]	August 28, 2014

[Results of review] Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with branch retinal vein occlusion has been demonstrated and its safety is acceptable in view of its observed benefits.

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

[Indication]

Age-related macular degeneration with subfoveal choroidal neovascularization
Macular edema secondary to ~~central~~ retinal vein occlusion
Choroidal neovascularization in pathologic myopia[1)]
Diabetic macular edema[1)]
(The strike-through denotes the text deleted in this application.)

[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 ~~central~~ 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.

(The strike-through denotes the text deleted in this application.)

[Condition for approval] The applicant is required to develop and appropriately implement a risk management plan.

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1) After this application was filed, a partial change application was approved for an additional indication of "choroidal neovascularization in pathologic myopia" on September 19, 2014, and for an additional indication of "diabetic macular edema" on November 18, 2014.

Review Report (1)

March 17, 2015

I. Product Submitted for Registration

[Brand name]	(a) Eylea Intravitreal Injection 40 mg/mL (b) Eylea Intravitreal Injection Kit 40 mg/mL
[Non-proprietary name]	Aflibercept (Genetical Recombination)
[Applicant]	Bayer Yakuhin, Ltd.
[Date of application]	August 28, 2014
[Dosage form/Strength]	(a) A solution for intravitreal injection containing 11.12 mg of Aflibercept (Genetical Recombination) per vial (0.278 mL) (b) A solution for intravitreal injection containing 6.6 mg of Aflibercept (Genetical Recombination) per syringe (0.165 mL)
[Proposed indication]	Age-related macular degeneration with subfoveal choroidal neovascularization Macular edema secondary to ~~central~~ retinal vein occlusion (The strike-through denotes the text deleted in this application.)
[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. Macular edema secondary to ~~central~~ retinal vein occlusion The dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL), administered by intravitreal injection. The dosing interval should be ≥1 month. (The strike-through denotes the text deleted in this application.)

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

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

Although this application is for a new indication, no new study has been conducted and neither "Data relating to quality" nor "Non-clinical data" have been submitted in this application because of the reasons that follow. Vascular endothelial growth factor (VEGF) has been suggested to be involved in macular edema secondary to branch retinal vein occlusion (BRVO) (Noma H et al. *Graefes Arch Clin Exp Ophthalmol.* 2006;244:309-315). In the initial application, thus, the following results from "Non-clinical data" as pharmacology data were submitted: Studies of binding affinity of Aflibercept (Genetical Recombination) (hereinafter referred to as aflibercept) for VEGF and placental growth factor (PlGF) (Attached documents 4.2.1.1-1 and 4.2.1.1-11 to the initial application), a study of aflibercept-induced inhibitions of human VEGF receptor phosphorylation and calcium mobilization (Attached document 4.2.1.1-3 to the initial application), a study of antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity of aflibercept (Attached document 4.2.1.1-4 to the initial application), studies of effects of aflibercept on choroidal and retinal neovascularization (Attached documents 4.2.1.1-7 and 4.2.1.1-9 to the initial application), and a study of effects of aflibercept on increased retinal vessel permeability (Attached document 4.2.1.1-8 to the initial application).

1. Origin or history of discovery, use in foreign countries, and other information

Retinal vein occlusion (RVO) is classified into 2 major categories: (i) central retinal vein occlusion (CRVO), characterized by venous occlusion near the optic disc; and (ii) branch retinal vein occlusion (BRVO), characterized by venous occlusion in branches of the retinal vein. RVO causes lesions such as retinal edema, retinal hemorrhage, and retinal ischemia distal to the site of occlusion. Among lesions associated with RVO, macular edema (retinal edema involving the macular area) is the primary cause of reduced visual acuity; visual prognosis in patients with macular edema secondary to BRVO is relatively good in general (Rehak J et al. *Curr Eye Res.* 2008;33:111-131), but foveal neovascularization induced by prolonged macular edema leads to irreversible changes in the macula with little prospect of recovery in visual acuity. In addition, vascular endothelial growth factor (VEGF) has been suggested to be involved in development of macular edema secondary to RVO (Campochiaro PA et al. *Ophthalmology.* 2009;116:2158-2164).

Aflibercept (Genetical Recombination) (hereinafter referred to as aflibercept) is a recombinant glycoprotein constructed by linking the extracellular domain of human VEGF receptor to the Fc domain of human immunoglobulin G1. In Japan, solution for intravitreal injection of aflibercept (hereinafter referred to as Eylea) was approved for the indication of "age-related macular degeneration (AMD) with subfoveal choroidal neovascularization" in September 2012, and for additional indications of "macular edema secondary to central retinal vein occlusion" in November 2013, "Choroidal neovascularization in pathologic myopia" in September 2014, and "Diabetic macular edema" in November 2014. The Japanese clinical studies were initiated in patients with macular edema secondary to BRVO in April 2012, and the applicant recently submitted a partial change approval application claiming that the efficacy and safety in patients with macular edema secondary to BRVO was demonstrated. As of February 2015, Eylea is approved for the indication of macular edema secondary to BRVO in the US and the EU.

2. Clinical data

2.(i) Summary of clinical pharmacology studies

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

The applicant submitted evaluation data resulting from a global phase III study (5.3.5.1.1, VIBRANT study) in patients with macular edema secondary to branch retinal vein occlusion (BRVO). Plasma concentrations of free aflibercept (unbound to VEGF) and bound aflibercept (aflibercept-VEGF complex) were determined by a method validated using enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantitation (LLOQ) of 15.6 ng/mL in the free form and 31.5 ng/mL in the bound form. A bridging immunoassay with detection sensitivity of 5.4 to 25.2 ng/mL was used for detection of serum anti-aflibercept antibodies [see "2.(ii) Summary of clinical efficacy and safety" for the study data on serum anti-aflibercept antibodies].

Study in patients (5.3.5.1.1, VIBRANT study)

Multiple intravitreal injections of aflibercept 2 mg were administered once every 4 weeks for 24 weeks (a total of 6 doses) to one eye of Japanese and non-Japanese patients with macular edema secondary to BRVO. Plasma concentrations of free aflibercept and bound aflibercept were as shown in Table 1, indicating no trend toward apparently inconsistent results with those concentrations in AMD patients with subfoveal choroidal neovascularization of the VIEW2 study[2)] and those concentrations in patients with central retinal vein occlusion (CRVO) of the GALILEO study.[3)]

The applicant's explanation:

Age, sex, BMI, renal function, and geographic factors are not likely to have significantly affected plasma aflibercept concentrations in the VIEW2[2)] and GALILEO studies.[3)] Given the data shown in Table 1, nor are these baseline characteristics likely to significantly affect plasma aflibercept concentrations in BRVO patients, although the plasma concentration data obtained from the VIBRANT study were inadequate due to the limited number of patients studied.

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2) Attached document 5.3.5.1-3 to the initial submission

3) Attached documents 5.3.5.1.3 and 5.3.5.1.4 to the partial change application for an additional indication of "macular edema secondary to CRVO"

Table 1. Plasma concentrations of free aflibercept and bound aflibercept in subjects after receiving intravitreal injections of aflibercept

Analyte	Time point	BRVO subjects (VIBRANT study)	CRVO subjects (GALILEO study)	AMD subjects (VIEW2 study)
Free aflibercept	Week 1	14.7 ± 14.8 (7/11) 0-49.4	-	4.74 ± 8.96 (39/169) 0-35.0
	Week 12	0 (0/11)	0 (0/84)	0.27 ± 2.51 (2/164) 0-27.8
Bound aflibercept	Week 1	142 ± 38.7 (11/11) 80.6-194	-	86.1 ± 46.5 (157/169) 0-239
	Week 12	168 ± 51.4 (11/11) 66.7-260	102 ± 48.7 (82/84) 0-220	128 ± 59.9 (160/164) 0-388
	Week 24	181 ± 60.3 (10/10) 80.3-296	118 ± 71.2 (16/16) 33.4-312	-

Upper data in each cell, Mean ± standard deviation (SD) (number of subjects with a concentration ≥ LLOQ/number of subjects evaluated)
Lower data in each cell, Minimum concentration-maximum concentration
Measured values below LLOQ were considered as 0 for calculation.

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

PMDA's view:

No new clinically relevant problems are likely to emerge in terms of the pharmacokinetics of aflibercept because no marked pharmacokinetic differences between patients with macular edema secondary to BRVO and secondary to CRVO were observed after intravitreal injections of Eylea.

2.(ii) Summary of clinical efficacy and safety

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

The applicant submitted efficacy and safety evaluation data resulting from a global phase III study (5.3.5.1.1, 5.3.5.1.11; VIBRANT study) in patients with macular edema secondary to BRVO.

No description of adverse events in any treatment group below denotes no adverse events reported in the group.

Global phase III study (5.3.5.1.1, 5.3.5.1.11; VIBRANT study [April 2012 to March 2014])

A randomized, double-masked, parallel-group, laser therapy-controlled, comparative study was conducted to evaluate the efficacy, safety, and pharmacokinetics of aflibercept in Japanese and non-Japanese patients with macular edema secondary to BRVO (target sample size of 180 [including 18 Japanese]; 90 in the laser group, 90 in the aflibercept group) [see "2.(i) Summary of clinical pharmacology studies" for pharmacokinetic data].

Subjects in the aflibercept group were to receive intravitreal injection of 2 mg of aflibercept in the study eye once every 4 weeks up to Week 20 (a total of 6 doses) and then once every 8 weeks from Week 24 to Week 48 (a total of 4 doses). Subjects in the laser group were to receive macular laser photocoagulation on the first day of the treatment.[4)] Subjects who meet the criteria for rescue therapy[5)] in the aflibercept group were to receive macular laser photocoagulation at Week 36, and subjects in the laser group were to receive laser therapy[6)] at Weeks 12, 16, and 20 as well as intravitreal injections of 2 mg of aflibercept from Week 24 to Week 48 (first once every 4 weeks injections [3 doses in total], then once every 8 weeks injections). All subjects with progression to clinically relevant intraocular

4) In order to maintain double-masking, subjects in the aflibercept group received a sham irradiation on the first day of the treatment and received a sham treatment (underwent the same procedure as an intravitreal injection except that an intravitreal injection was not performed while a needleless syringe was applied to the eyeball under local anesthesia instead) once every 8 weeks from Week 28 to Week 44 (a total of 3 sham treatments). Subjects in the laser group received a sham treatment on the first day of the treatment, and once every 4 weeks from Week 4 to Week 48 (a total of 12 treatments). Subjects who met the criteria for rescue therapy received a predefined laser therapy or aflibercept treatment.

5) The rescue therapy was performed in subjects who met one or more of the following criteria at Week 12 or later:
- The central retinal thickness (CRT) determined by optical coherence tomography (OCT) increased by >50 μm from the previous lowest value.
- New or persistent retinal cystic change or subretinal fluid was detected by OCT, or a persistent diffuse edema was detected by OTC in the central subfield.
- The best corrected visual acuity (BCVA) score decreased by ≥5 letters from the previous highest score, and the CRT determined by OCT increased from the previous best value.

6) The laser therapy was performed only in subjects who received the last laser therapy ≥12 weeks ago.

neovascularization[7] were allowed to receive peripheral scatter laser photocoagulation at any time during the study. The observation period was to be 52 weeks.

All of the 183 subjects treated (92 subjects [including 10 Japanese subjects] in the laser group, 91 subjects [including 11 Japanese subjects] in the aflibercept group) were included in the safety analysis population, of whom 181 subjects (90 subjects [including 9 Japanese subjects] in the laser group, 91 subjects [including 11 Japanese subjects] in the aflibercept group) excluding 2 subjects (both in the laser group) who did not have a best corrected visual acuity (BCVA) score[8] after study treatment were included in the full analysis set (FAS). Study treatment was discontinued in a total of 15 subjects (9 subjects in the laser group, 6 subjects in the aflibercept group) by Week 24 and 33 subjects (15 subjects in the laser group, 18 subjects in the aflibercept group) by Week 52. The main reasons for discontinuation by Week 24 included consent withdrawal (9 subjects; 6 subjects in the laser group, 3 subjects in the aflibercept group) and adverse events (3 subjects in the aflibercept group).

The number of aflibercept injections (mean ± standard deviation [SD] [minimum-maximum]) throughout the study period (52 weeks) in the safety analysis set was 4.4 ± 1.0 (1-5) doses in the laser group and 9.0 ± 1.8 (2-10) doses in the aflibercept group.

The proportion[9] of subjects in the FAS who gained ≥15 letters in BCVA score from baseline at Week 24 (the primary endpoint) was 26.7% (24 of 90 subjects) in the laser group and 52.7% (48 of 91 subjects) in the aflibercept group. The treatment difference (95% confidence interval [CI]) between the aflibercept and laser groups was 26.6% (13.0, 40.1), showing a statistically significant difference (P = 0.0003, Cochran-Mantel-Haenszel test adjusted by geographic location[10] and baseline BCVA score category[11]). The time courses of BCVA score from baseline to Week 52 in the FAS were as shown in Figure 1.

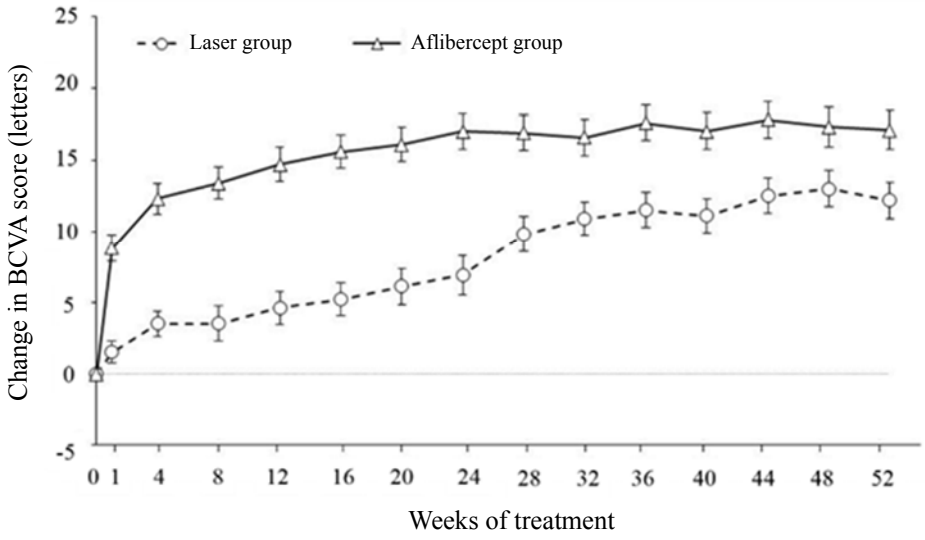

Figure 1. Time courses of BCVA score from baseline
(Mean ± standard error [SE], VIBRANT study, FAS, LOCF)

Adverse events (including laboratory abnormalities)[12] were reported by 75 of 92 subjects (81.5%) in the laser group and 76 of 91 subjects (83.5%) in the aflibercept group; the incidence among Japanese subjects was 60.0% (6 of 10 subjects) in the laser group and 72.7% (8 of 11 subjects) in the aflibercept group. One death was reported in the laser group; the subject died of pneumonia 35 days after the last

7) Defined, for example, as retinal neovascularization of ≥5-fold optic disc diameter with intravitreal haemorrhage, disc neovascularization, or neovascularization in the anterior segment of the eye
8) Measured using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart (at a distance of 4 m)
9) Last Observation Carried Forward (LOCF) was used to impute missing values in subjects who had no BCVA score at Week 24.
10) North America or Japan
11) Categorized as >20/200 (≥35 letters) or ≤20/200 (≤34 letters)
12) MedDRA ver. 16.1

laser therapy. This subject did not receive aflibercept injection, and a causal relationship to the study drug was ruled out. Other serious adverse events are shown in Table 2. Of these, a causal relationship to the injection procedure could not be ruled out for 1 event (cataract traumatic) reported in 1 subject of the aflibercept group. Study treatment was discontinued in 3 subjects in the aflibercept group due to an adverse event (breast cancer metastatic, cataract traumatic, and intraocular pressure increased [1 subject each]; intraocular pressure increased was reported by a Japanese subject). Of these, a causal relationship to the study drug could not be ruled out for intraocular pressure increased (1 subject) in the aflibercept group.

Table 2. Serious adverse events (VIBRANT study, safety analysis set)

Laser group (10 subjects including 1 Japanese subject)	Cardiac failure acute/myocardial infarction, dehydration/hypomagnesaemia/cervical spinal stenosis/cerebrovascular accident/renal failure acute/aortic stenosis, non-cardiac chest pain, road traffic accident/subarachnoid haemorrhage, dehydration/hypertension, syncope, osteomyelitis/pneumonia/osteonecrosis/renal failure, spinal column stenosis, hernia, and atrial flutter* (1 subject each)
Aflibercept group (14 subjects including 1 Japanese subject)	Squamous cell carcinoma/hypertension, chest pain/hypoaesthesia, atrial fibrillation/cardiomyopathy/coronary artery disease, lung adenocarcinoma, anaemia/gastritis, hydronephrosis/nephrolithiasis, breast cancer metastatic/renal failure acute, anaemia/intestinal fistula/small intestinal obstruction/pelvic abscess/pneumonia/delayed haemolytic transfusion reaction/presyncope, gastroenteritis, pyelonephritis/transaminases increased, atrioventricular block second degree/bradycardia, pneumonia, cataract traumatic, and large intestine polyp* (1 subject each)

*: Reported by a Japanese subject.
Serious adverse events are presented by subject; adverse events combined with a slash(es) were reported by the sane subject.

Adverse events for which a causal relationship to the study drug could not be ruled out (including laboratory abnormalities) were reported by 4 of 92 subjects (4.3%) in the laser group (eye discharge/eye irritation, eye discharge/eye pain/ocular hyperaemia, blood pressure increased, and hypertension [1 subject each]) and 5 of 91 subjects (5.5%) in the aflibercept group (intraocular pressure increased, retinal vascular disorder, glucose urine present/proteinuria/blood urine present, blood creatinine increased, and hypertension [1 subject each]; of these, intraocular pressure increased and glucose urine present/proteinuria/blood urine present were reported by 1 Japanese subject each).

Changes in vital signs (blood pressure, heart rate, body temperature) were reported as adverse events by 26 of 92 subjects (28.3%) in the laser group and 19 of 91 subjects (20.9%) in the aflibercept group. Of these, a causal relationship to the study drug could not be ruled out for 2 events (blood pressure increased, hypertension [1 subject each]) in the laser group and 1 event (hypertension [1 subject]) in the aflibercept group.

The proportion[13)] of subjects who developed anti-aflibercept antibodies was 1.1% (1 of 91 subjects) in the laser group[14)] and 1.1% (1 of 90 subjects) in the aflibercept group.[15)]

The applicant's explanation:
Based on the above, in Japanese and non-Japanese patients with macular edema secondary to BRVO, treatment with aflibercept 2 mg injected intravitreally once every 4 weeks (a total of 6 doses) was demonstrated to be superior to laser therapy in terms of the proportion of patients who gained ≥15 letters in BCVA score from baseline at Week 24, and to be well tolerated during the treatment period through Week 52.

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

2.(ii).B.(1) Clinical positioning of aflibercept

PMDA asked the applicant to explain the clinical positioning of aflibercept in light of differences in the pathogenesis and treatment strategies between BRVO and CRVO.

13) The number of subjects who are anti-aflibercept antibody positive up to Week 52/the number of subjects evaluated
14) This subject received aflibercept after Week 24.
15) The proportion of subjects who developed anti-aflibercept antibodies did not substantially differ from that among patients with CRVO, and nor has clear impact of anti-aflibercept antibodies on the efficacy or safety been observed among patients with macular edema secondary to BRVO.

The applicant's explanation:
Although different veins are involved in BRVO and CRVO, both diseases have the same pathogenesis in which thrombotic vein occlusion leads to retinal hemorrhage and retinal edema in the macular area, and are associated with upregulation of intraocular VEGF, which is highly related to the pathogenesis of macular edema (Funk M et al. *Invest Ophthalmol Vis Sci.* 2009;50:1025-1032). Foreign epidemiologic studies have identified hypertension, diabetes mellitus, aging (≥65 years), renal disease, dyslipidemia, coagulation disorder, and smoking as systemic risk factors for CRVO (The Eye Disease Case-Control Study Group. *Arch Ophthalmol.* 1996;114:545-554, Kolar P. *J Ophthalmol.* 2014;1-5, Channa R et al. *Clin Ophthalmol.* 2011;5:705-713, Wong TY et al. *N Engl J Med.* 2010;363:2135-2144), and glaucoma as an ocular risk factor for CRVO (Kolar P. *J Ophthalmol.* 2014;1-5, Wong TY et al. *N Engl J Med.* 2010;363:2135-2144). Likewise, studies have identified hypertension, dyslipidemia, peripheral arterial disorder, and metabolic disorder such as diabetes mellitus as main risk factors for BRVO (Kolar P. *J Ophthalmol.* 2014;1-5). The natural course of visual acuity in patients with CRVO has been considered to depend on baseline visual acuity; visual acuity was not improved from baseline in 80% of patients with baseline visual acuity of ≤0.1 but was maintained in 65% of patients with baseline visual acuity of ≥0.5 (The Central Vein Occlusion Study Group. *Arch Ophthalmol.* 1997;115:486-491). On the other hand, BRVO patients showed mild or moderate[16)] vision loss at baseline, and, they experienced improvement in the time course more frequently than worsening. However, few patients achieved corrected visual acuity of >20/40 (Rogers SL et al. *Ophthalmology.* 2010;117:1094-1101).

Therapeutic approaches for macular edema secondary to RVO include macular laser photocoagulation, intravitreal injection of glucocorticoid, and surgical treatment, but macular laser photocoagulation is not recommended for the treatment of CRVO (The Central Vein Occlusion Study Group. *Ophthalmology.* 1995;102:1425-1433). In contrast, macular laser photocoagulation has been the standard care for patients with BRVO for many years (The Branch Vein Occlusion Study Group. *Am J Ophthalmol.* 1984;98:271-282, Chatziralli IP et al. *Semin Ophthalmol.* 2014;29:85-107). However, macular laser photocoagulation has been reported to have the following drawbacks: having limited efficacy with slow improvement of visual acuity; and being inapplicable to lesions in the foveal avascular zone due to its potentially causing absolute scotoma by its irreversible damaging of photoreceptors (The Branch Vein Occlusion Study Group. *Am J Ophthalmol.* 1984;98:271-282). With this background, since the intraocular VEGF levels increase in both patients with BRVO and CRVO, the usefulness of anti-VEGF agents was also expected in treatment of RVO. This resulted in the regulatory approval of ranibizumab (genetical recombination), an anti-VEGF agent, for the indication of macular edema secondary to RVO in the US (in 2010), EU (in 2011), and Japan (in 2013), rendering it a potential first-line therapy for RVO, although the optimal treatment regimen has not been established. Given the efficacy and safety in CRVO patients demonstrated by clinical studies (the GALILEO[3)] and COPERNICUS[17)] studies), aflibercept may also be a therapeutic drug effective for macular edema secondary to BRVO as well as to CRVO.

PMDA's view:
Although different veins are involved in BRVO and CRVO, increased intraocular VEGF levels are related to the pathogenesis of macular edema secondary to BRVO and CRVO. Aflibercept, an anti-VEGF agent, has been demonstrated to be effective and safe in clinical studies (the GALILEO[3)] and COPERNICUS[17)] studies) conducted in patients with macular edema secondary to CRVO, while ranibizumab (genetical recombination), an anti-VEGF agent, has already been emerging as a potential first-line therapy for macular edema secondary to RVO. Given the above situation, aflibercept can become a new therapeutic option for macular edema secondary to BRVO.

2.(ii).B.(2) Evaluation based on global study data

2.(ii).B.(2).1) Intrinsic and extrinsic ethnic factors

Given the fact that the VIBRANT study in Japanese patients with macular edema secondary to BRVO was conducted as a global study, PMDA asked the applicant to explain the intrinsic and extrinsic ethnic factors that may affect the efficacy and safety of aflibercept.

16) Defined as having a visual acuity of 20/40 measured with Snellen eye chart
17) Attached documents 5.3.5.1.1 and 5.3.5.1.2 to a partial change application for an additional indication of "macular edema secondary to CRVO"

The applicant's explanation:

- Aflibercept is unlikely to be affected by ethnic differences of pharmacokinetic origin because it is a protein preparation that is not affected by drug metabolizing enzymes and is intended for local intravitreal injection.

- The prevalence of BRVO overseas has been reported to be 0.2% to 2.0% regardless of geographic location or race (Laouri M et al. *Eye.* 2011;25:981-988); in Japan, the prevalence has been reported to be 2.0% to 2.7% in the Hisayama cohort study (Yasuda M et al. *Invest Ophthalmol Vis Sci.* 2010;51:3205-3209, Arakawa S et al. *Invest Ophthalmol Vis Sci.* 2011;52:5905-5909) and 0.47% in the Funagata cohort study (Kawasaki R et al. *Ophthalmology.* 2008;115:917-919), showing no apparent difference between data in Japan and overseas.

- BRVO is mainly classified into the first-order (temporal vein occlusion) and the second-order (macular vein occlusion) subtypes based on the site of occluded arteriovenous crossing (Rehak J et al. *Curr Eye Res.* 2008;33:111-131); the first-order subtype has been reported to account for 63% in Japan and 61% overseas, and the second-order subtype has been reported to account for 15% and 28%, respectively (Tobari I. *Retinal vein occlusion.* Medical-Aoi Publications, Inc.; 2002, Clemett RS et al. *Trans Ophthalmol Soc.* 1973;93:523-535).

- Among symptoms associated with BRVO, macular edema and neovascularization have been considered to affect visual prognosis. The incidence of macular edema has been reported to be approximately 50% in Japan (Kita M. *Today's therapy in ophthalmology.* Igaku-Shoin Ltd.; 2007) and 60% overseas (Rehak J et al. *Curr Eye Res.* 2008;33:111-131), and the incidence of neovascularization has been reported to be approximately 27% in Japan (Takahashi M et al. *Japanese Journal of Ophthalmology.* 1981;85:731-736) and 20% to 30% overseas (The Branch Vein Occlusion Study Group. *Arch Ophthalmol.* 1986;104:34-41).

- Since diagnostic criteria for BRVO have not yet been established, visual acuity testing, funduscopic examination, evaluation of circulatory condition by fluorescein angiography, and evaluation of macular edema by optical coherence tomography (OCT) have been used for its diagnosis.

- Although ranibizumab (genetical recombination) was approved in the US (June 2010) and Canada (August 2011) as a medical treatment for macular edema secondary to BRVO before the initiation of the VIBRANT study (April 2012), macular laser photocoagulation, not ranibizumab, was considered as the standard therapy at that time in and out of Japan.

Based on the above, there was no substantial difference in the intrinsic and extrinsic ethnic factors among the studied regions, and therefore, the VIBRANT study was conducted appropriately as a global study.

2.(ii).B.(2).2) Consistency of study data between non-Japanese and Japanese populations

PMDA asked the applicant to explain the consistency of data between non-Japanese and Japanese populations in the VIBRANT study.

The applicant's explanation:

The proportion of subjects who gained ≥15 letters in BCVA score from baseline, the change in BCVA score from baseline, and the change in central retinal thickness (CRT) from baseline were as shown in Table 3 for the efficacy data. Although there was a trend toward a smaller efficacy in the Japanese population than in the non-Japanese population in both laser and aflibercept treatment groups in terms of the proportion of patients who gained ≥15 letters in BCVA score from baseline at Week 24 and the change in BCVA score from baseline, no substantial treatment difference was seen between treatment groups in any population. In addition, based on the time courses of BCVA score (Figure 2), improvement of visual acuity at an early phase of treatment was smaller in the Japanese population than in the non-Japanese population, possibly affected by the difference in distribution of patient characteristics between the 2 populations, although the definite cause has not yet been identified. In terms of the change in CRT from baseline, the improvement in the laser group was greater in the non-Japanese population, while that in the aflibercept group was greater in the Japanese population, possibly affected by differences in the distributions of baseline CRT values and patients' age. However, there is no particular problem

because the improvement was greater in the aflibercept group than in the laser group in both populations.

Table 3. Proportion of subjects who gained ≥15 letters of visual acuity from baseline at Week 24 or 52 and changes in BCVA score and CRT from baseline (VIBRANT study, FAS)

			Laser group	Aflibercept group	Between-group difference [95% CI]
Number of subjects evaluated		Whole population	90	91	-
		Japanese	9	11	-
		Non-Japanese	81	80	-
BCVA score at baseline (mean ± SD)		Whole population	57.7 ± 11.3	58.6 ± 11.4	-
		Japanese	54.4 ± 14.0	57.6 ± 12.6	-
		Non-Japanese	58.1 ± 11.0	58.8 ± 11.3	-
Percentage of patients who gained ≥15 letters of visual acuity from baseline (number of subjects)[a)]	Week 24	Whole population	26.7 (24)	52.7 (48)	26.6 [13.0, 40.1][b)]
		Japanese	11.1 (1)	36.4 (4)	25.3 [-19.1, 62.5]
		Non-Japanese	28.4 (23)	55.0 (44)	26.6 [10.8, 41.0]
	Week 52	Whole population	41.1 (37)	57.1 (52)	16.2 [2.0, 30.5] [b)]
		Japanese	33.3 (3)	45.5 (5)	12.1 [-32.4, 53.6]
		Non-Japanese	42.0 (34)	58.8 (47)	16.8 [1.0, 32.0]
Change in BCVA score from baseline (mean ± SD)[a)]	Week 24	Whole population	6.9 ± 12.9	17.0 ± 11.9	10.5 [7.1, 14.0][c)]
		Japanese	2.4 ± 9.7	12.5 ± 8.0	10.7 [2.4, 18.9][d)]
		Non-Japanese	7.4 ± 13.2	17.6 ± 12.2	10.5 [6.7, 14.2][d)]
	Week 52	Whole population	12.2 ± 11.9	17.1 ± 13.1	5.2 [1.7, 8.7][c)]
		Japanese	9.1 ± 9.1	14.9 ± 6.6	6.3 [-1.2, 13.7][d)]
		Non-Japanese	12.6 ± 12.2	17.4 ± 13.7	5.0 [1.2, 8.9][d)]
CRT at baseline (μm) (mean ± SD)		Whole population	553.5 ± 188.1	558.9 ± 185.9	-
		Japanese	657.7 ± 193.7	587.4 ± 110.7	-
		Non-Japanese	541.9 ± 185.1	555.0 ± 194.2	-
Changes in CRT from baseline (μm) (mean ± SD)[a)]	Week 24	Whole population	-128.0 ± 195.0	-280.5 ± 189.7	-148.6 [-179.8, -117.4][e)]
		Japanese	-93.1 ± 116.2	-317.9 ± 121.3	-260.0 [-351.4, -168.7][f)]
		Non-Japanese	-131.9 ± 202.0	-275.3 ± 197.3	-131.6 [-163.6, -99.5][f)]
	Week 52	Whole population	-249.3 ± 189.8	-283.9 ± 189.1	-29.5 [-54.7, -4.4][e)]
		Japanese	-271.7 ± 195.1	-319.3 ± 120.5	-87.8 [-219.9, 44.3][f)]
		Non-Japanese	-246.8 ± 190.3	-279.1 ± 196.7	-20.0 [-44.0, 4.0][f)]

a) Missing values were imputed by using the LOCF method.
b) Adjusted by using Mantel-Haenszel weight with region and baseline BCVA score category as the strata
c) Calculated based on an analysis of a covariance (ANCOVA) model with the treatment group, region, and baseline BCVA score category as fixed effects and baseline BCVA score as covariate
d) Calculated based on an ANCOVA model with the treatment group as fixed effect and baseline BCVA score category as covariate
e) Calculated based on an ANCOVA model with the treatment group, region, and baseline BCVA score category as fixed effects and the baseline CRT value as covariate.
f) Calculated based on an ANCOVA model with the treatment group as fixed effect and the baseline CRT value as covariate.

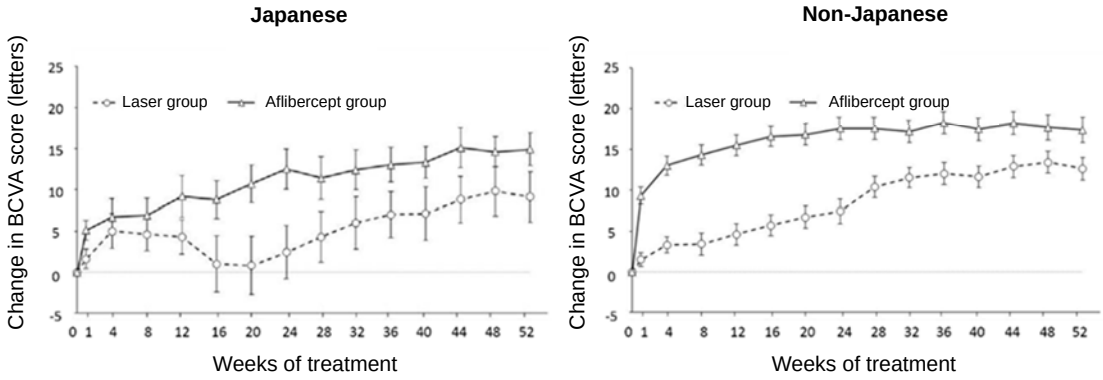

Figure 2. Time courses of BCVA score from baseline to Week 52
(Mean ± SE, VIBRANT study, FAS, LOCF)

In addition, no substantial population difference was seen in the number of aflibercept injections during the period up to Week 24 or during the period from after Week 24 to Week 52, as shown in Table 4.

Table 4. Numbers of aflibercept injections and laser therapies during the period up to Week 24 and during the period from after Week 24 to Week 52 (VIBRANT study, FAS)

			Laser[a] group or laser + aflibercept[b] group	Aflibercept group
Up to Week 24	Number of subjects evaluated	Whole population	90	91
		Japanese	9	11
		Non-Japanese	81	80
	Number of aflibercept injections	Whole population	0	5.7 ± 0.8 (91)
		Japanese	0	5.7 ± 0.6 (11)
		Non-Japanese	0	5.7 ± 0.8 (80)
	Number of laser therapies	Whole population	1.7 ± 0.5 (90)	0
		Japanese	1.6 ± 0.5 (9)	0
		Non-Japanese	1.7 ± 0.5 (81)	0
From after Week 24 to Week 52[c]	Number of subjects evaluated	Whole population	83	85
		Japanese	7	10
		Non-Japanese	76	75
	Number of aflibercept injections	Whole population	4.4 ± 1.0 (67)	3.6 ± 0.8 (84)
		Japanese	4.9 ± 0.4 (7)	4.0 ± 0.0 (10)
		Non-Japanese	4.4 ± 1.1 (60)	3.6 ± 0.8 (74)
	Number of laser therapies	Whole population	1.0 (1)	1.0 ± 0.0 (9)
		Japanese	0	0
		Non-Japanese	1.0 (1)	1.0 ± 0.0 (9)

Mean ± SD (number of subjects evaluated)
a) Up to Week 24
b) From after Week 24 to Week 52
c) Subjects who completed 24 weeks of treatment were included.

The incidences of adverse events in the whole, Japanese, and non-Japanese populations in the VIBRANT study are shown in Table 5, and safety issues requiring particular attention in the Japanese population are unlikely to arise because no substantial difference in adverse events was seen between non-Japanese and Japanese populations. The incidences of adverse events related to the injection procedure and of conjunctival haemorrhage were slightly higher up to Week 24 than during the period from after Week 24 to Week 52, possibly due to the difference in the number of aflibercept injections (mean number of injections in the whole population: 5.7 doses up to Week 24; 3.6 doses during the period from after Week 24 to Week 52). The incidence of other adverse events was not markedly different regardless of the periods studied.

Consequently, the applicant considered that the efficacy and safety of aflibercept in the Japanese population can be evaluated based on the data from the VIBRANT study.

Table 5. Incidence of adverse events (VIBRANT study, safety analysis set)

			Up to Week 24		From after Week 24 to Week 52[a)]	
			Laser group	Aflibercept group	Laser + aflibercept group	Aflibercept group
Number of subjects evaluated		Whole population	92	91	83	85
		Japanese	10	11	7	10
		Non-Japanese	82	80	76	75
All adverse events		Whole population	54 (58.7)	58 (63.7)	62 (74.7)	58 (68.2)
		Japanese	6 (60.0)	6 (54.5)	2 (28.6)	7 (70.0)
		Non-Japanese	48 (58.5)	52 (65.0)	60 (78.9)	51 (68.0)
Adverse events in the study eye		Whole population	25 (27.2)	34 (37.4)	35 (42.2)	30 (35.3)
		Japanese	2 (20.0)	2 (18.2)	2 (28.6)	0
		Non-Japanese	23 (28.0)	32 (40.0)	33 (43.4)	30 (40.0)
Adverse events in the contralateral eye		Whole population	7 (7.6)	10 (11.0)	12 (14.5)	14 (16.5)
		Japanese	2 (20.0)	1 (9.1)	1 (14.3)	0
		Non-Japanese	5 (6.1)	9 (11.3)	11 (14.5)	14 (18.7)
Non-ocular adverse events		Whole population	46 (50.0)	43 (47.3)	45 (54.2)	41 (48.2)
		Japanese	5 (50.0)	5 (45.5)	2 (28.6)	7 (70.0)
		Non-Japanese	41 (50.0)	38 (47.5)	43 (56.6)	34 (45.3)
Death		Whole population	1 (1.1)	0	0	0
		Japanese	0	0	0	0
		Non-Japanese	1 (1.2)	0	0	0
Serious adverse events excluding death		Whole population	8 (8.7)	8 (8.8)	3 (3.6)	7 (8.2)
		Japanese	1 (10.0)	0	0	1 (10.0)
		Non-Japanese	7 (8.5)	8 (10.0)	3 (3.9)	6 (8.0)
Adverse events leading to treatment discontinuation		Whole population	0	3 (3.3)	0	0
		Japanese	0	1 (9.1)	0	0
		Non-Japanese	0	2 (2.5)	0	0
Adverse events related to the study drug		Whole population	3 (3.3)	2 (2.2)	2 (2.4)	4 (4.7)
		Japanese	0	2 (18.2)	0	1 (10.0)
		Non-Japanese	3 (3.7)	0	2 (2.6)	3 (4.0)
Adverse events related to injection procedure		Whole population	8 (8.7)	23 (25.3)	15 (18.1)	14 (16.5)
		Japanese	0	0	1 (14.3)	0
		Non-Japanese	8 (9.8)	23 (28.8)	14 (18.4)	14 (18.7)
Main adverse events[b)]	Conjunctival haemorrhage	Whole population	5 (5.4)	18 (19.8)	11 (13.3)	9 (10.6)
		Japanese	1 (10.0)	0	0	0
		Non-Japanese	4 (4.9)	18 (22.5)	11 (14.5)	9 (12.0)
	Hypertension	Whole population	10 (10.9)	6 (6.6)	8 (9.6)	4 (4.7)
		Japanese	0	1 (9.1)	1 (14.3)	0
		Non-Japanese	10 (12.2)	5 (6.3)	7 (9.2)	4 (5.3)
	Nasopharyngitis	Whole population	5 (5.4)	6 (6.6)	4 (4.8)	4 (4.7)
		Japanese	3 (30.0)	0	1 (14.3)	1 (10.0)
		Non-Japanese	2 (2.4)	6 (7.5)	3 (3.9)	3 (4.0)

Number of subjects with events (Incidence %)

a) Subjects who completed 24 weeks of treatment were included

b) Defined as adverse events with an incidence of ≥10% reported by more than 1 subject in either group.

PMDA's view:

Aflibercept is a protein preparation that is locally administered by intravitreal injection and is not affected by drug metabolizing enzymes. The pathogenesis and prevalence of BRVO, as well as its diagnostic criteria and concept on standard therapies, do not substantially differ between Japan and overseas. Therefore, there is no substantial difference in the intrinsic and extrinsic ethnic factors that affect the efficacy and safety of aflibercept. In addition, although the number of Japanese patients studied was limited, efficacy of aflibercept has been demonstrated, almost equally between non-Japanese and Japanese populations, in the VIBRANT study. Furthermore, no substantial difference in the safety has been observed between non-Japanese and Japanese populations. Consequently, there is no problem with reviewing the efficacy and safety of aflibercept in Japanese patients with BRVO based on the data of the VIBRANT study.

2.(ii).B.(3) Factors affecting the efficacy of aflibercept

PMDA asked the applicant to explain the factors affecting the efficacy of aflibercept.

The applicant's explanation:

Table 6 shows the proportion of patients who gained ≥15 letters in BCVA score and the change in BCVA score from baseline at Week 24 by patient characteristics in the VIBRANT study together with those in the GALILEO[3)] and COPERNICUS studies.[17)] In the VIBRANT study, no consistent trend was found between the patient characteristics and the between-group difference in the proportion of patients who

gained ≥15 letters in BCVA score or in the change in BCVA score from baseline at Week 24. In addition, the factors that affect the efficacy of aflibercept did not exert any markedly different influence on BRVO patients in the VIBRANT study and CRVO patients in the phase III studies in patients with macular edema secondary to CRVO (the GALILEO[3)] and COPERNICUS[17)] studies).

Table 6. Proportion of subjects who gained ≥15 letters in BCVA score from baseline at Week 24 and the change in BCVA score from baseline by patient characteristics (FAS)

		VIBRANT study		COPERNICUS study		GALILEO study	
		Laser group	Aflibercept group	Sham group	Aflibercept group	Sham group	Aflibercept group
Sex	Male	27.8 (15/54) 6.6 ± 13.3	52.3 (23/44) 18.2 ± 11.5	18.4 (7/38) -0.3 ± 16.9	58.0 (40/69) 19.2 ± 13.3	29.7 (11/37) 4.4 ± 14.7	65.5 (38/58) 18.0 ± 12.9
	Female	25.0 (9/36) 7.4 ± 12.4	53.2 (25/47) 15.8 ± 12.2	5.7 (2/35) -8.1 ± 18.5	53.3 (24/45) 14.5 ± 11.5	12.9 (4/31) 2.0 ± 13.4	53.3 (24/45) 18.1 ± 11.3
Age	<65 years	36.2 (17/47) 10.8 ± 11.6	68.4 (26/38) 20.4 ± 12.6	10.3 (3/29) -3.7 ± 16.9	67.3 (33/49) 19.5 ± 12.6	35.5 (11/31) 5.6 ± 17.3	67.9 (38/56) 19.7 ± 10.9
	≥65 and <75 years	18.5 (5/27) 2.3 ± 14.7	43.8 (14/32) 14.5 ± 8.3	21.1 (4/19) 1.3 ± 16.2	47.1 (16/34) 16.5 ± 12.4	9.5 (2/21) 3.0 ± 9.6	47.5 (19/40) 15.4 ± 13.0
	≥75 years	12.5 (2/16) 3.4 ± 10.1	38.1 (8/21) 14.6 ± 14.0	8.0 (2/25) -8.5 ± 19.8	48.4 (15/31) 14.8 ± 13.3	12.5 (2/16) -0.8 ± 11.6	71.4 (5/7) 20.1 ± 15.9
BCVA score at baseline[a)]	≤34 letters/ ≤35 letters	28.6 (2/7) 7.3 ± 11.8	66.7 (4/6) 34.5 ± 22.3	16.7 (3/18) 0.0 ± 13.6	67.9 (19/28) 21.9 ± 14.2	25.0 (3/12) 4.8 ± 10.6	64.7 (11/17) 21.1 ± 16.2
	≥35 letters/ ≥36 letters	26.5 (22/83) 6.9 ± 13.1	51.8 (44/85) 15.7 ± 9.9	10.9 (6/55) -5.4 ± 19.1	52.3 (45/86) 15.9 ± 12.0	21.4 (12/56) 3.0 ± 14.8	59.3 (51/86) 17.4 ± 11.2
Retinal perfusion status at baseline[b)]	Non-ischemic	24.2 (15/62) 5.7 ± 13.2	43.6 (24/55) 14.3 ± 9.0	16.0 (8/50) -4.8 ± 19.7	59.7 (46/77) 17.1 ± 12.7	25.9 (14/54) 6.0 ± 13.4	61.8 (55/89) 17.8 ± 12.0
	Ischemic	37.5 (6/16) 11.3 ± 11.0	60.0 (12/20) 19.1 ± 13.7	0 (0/12) 1.5 ± 11.5	41.2 (7/17) 13.3 ± 12.6	0 (0/7) -11.7 ± 12.9	57.1 (4/7) 17.1 ± 16.1
Duration of disease[c)]	<3 months	29.2 (21/72) 7.3 ± 13.7	53.3 (40/75) 17.3 ± 12.7	14.5 (9/62) -4.3 ± 18.9	70.1 (54/77) 19.6 ± 12.8	19.5 (8/41) 2.1 ± 15.1	67.6 (48/71) 18.8 ± 12.6
	≥3 months	27.3 (3/11) 5.8 ± 11.7	42.9 (3/7) 13.4 ± 5.4	0 (0/11) -2.6 ± 11.4	30.6 (11/36) 12.1 ± 11.2	25.9 (7/27) 5.2 ± 12.4	46.7 (14/30) 16.2 ± 11.4

Upper data in each cell: Percentage of subjects who gained ≥15 letters of visual acuity from baseline at Week 24 (number of patients who experienced improvement/number of subjects evaluated)
Lower data in each cell: Change in BCVA score from baseline to Week 24 (mean ± SD)
Missing values were imputed by using the LOCF method.
a) Improvement was categorized into ≤34 letters or ≥35 letters in the VIBRANT study, and into ≤35 letters or ≥36 letters in the COPERNICUS and GALILEO studies.
b) Subjects were excluded if their data were unevaluable or their relevant data were missing.
c) Subjects were excluded if their relevant data were missing.

PMDA's view:
These patient characteristics are unlikely to significantly affect the efficacy of aflibercept because the results of any subgroup analysis of the VIBRANT study consistently showed a higher efficacy of aflibercept over laser therapy. In addition, no substantial difference was observed in how these factors affect the efficacy of aflibercept between the treatments in BRVO and CRVO patients.

2.(ii).B.(4) Safety

2.(ii).B.(4).1) Comparison of safety profiles of aflibercept in patients with macular edema secondary to BRVO and with macular edema secondary to CRVO

PMDA asked the applicant to compare the safety profiles of aflibercept in patients with macular edema secondary to BRVO and with macular edema secondary to CRVO, the latter of which is an already approved indication.

The applicant's explanation:
Table 7 shows the incidences of adverse events in the phase III studies in patients with macular edema secondary to CRVO (the GALILEO[3)] and COPERNICUS[17)] studies) and in the VIBRANT study. The incidences of all adverse events and of adverse events in the study eye in the aflibercept group tended to be slightly lower in BRVO subjects than in CRVO subjects. The incidence or type of overall adverse

events and adverse events related to VEGF inhibition (Table 8) did not tend to differ between CRVO and BRVO subjects. BRVO-specific safety issues are unlikely to arise.

Based on the above, there was no substantial difference in the safety profile of aflibercept between CRVO and BRVO patients.

Table 7. Incidence of adverse events up to Week 52 in clinical studies in CRVO and BRVO subjects (safety analysis set)

		BRVO subjects (VIBRANT study)		CRVO subjects (GALILEO and COPERNICUS studies)		
		Laser group	Aflibercept group	Sham group[a)]	Sham group[b)]	Aflibercept group[c)]
Number of subjects evaluated		92	91	68	74	218
All adverse events		75 (81.5)	76 (83.5)	59 (86.8)	68 (91.9)	197 (90.4)
Adverse events in the study eye		44 (47.8)	45 (49.5)	49 (72.1)	58 (78.4)	168 (77.1)
Adverse events in the contralateral eye		18 (19.6)	23 (25.3)	13 (19.1)	28 (37.8)	60 (27.5)
Non-ocular adverse events		63 (68.5)	61 (67.0)	45 (66.2)	54 (73.0)	154 (70.6)
Death		1 (1.1)	0	0	1 (1.4)	0
Serious adverse events excluding death		10 (10.9)	14 (15.4)	13 (19.1)	21 (28.4)	40 (18.3)
Adverse events leading to treatment discontinuation		0	3 (3.3)	7 (10.3)	5 (6.8)	8 (3.7)
Adverse events related to the study drug		4 (4.3)	5 (5.5)	6 (8.8)	4 (5.4)	15 (6.9)
Adverse events related to the injection procedure		19 (20.7)	27 (29.7)	21 (30.9)	20 (27.0)	78 (35.8)
Major adverse events[d)]	Conjunctival haemorrhage	15 (16.3)	22 (24.2)	3 (4.4)	15 (20.3)	32 (14.7)
	Eye irritation	1 (1.1)	7 (7.7)	7 (10.3)	4 (5.4)	14 (6.4)
	Eye pain	9 (9.8)	6 (6.6)	4 (5.9)	7 (9.5)	33 (15.1)
	Macular oedema	3 (3.3)	1 (1.1)	16 (23.5)	1 (1.4)	47 (21.6)
	Retinal exudates	2 (2.2)	0	7 (10.3)	4 (5.4)	21 (9.6)
	Retinal haemorrhage	2 (2.2)	4 (4.4)	9 (13.2)	10 (13.5)	28 (12.8)
	Retinal vascular disorder	2 (2.2)	1 (1.1)	8 (11.8)	6 (8.1)	21 (9.6)
	Visual acuity reduced	1 (1.1)	1 (1.1)	8 (11.8)	16 (21.6)	33 (15.1)
	Vitreous haemorrhage	3 (3.3)	1 (1.1)	2 (2.9)	9 (12.2)	9 (4.1)
	Nasopharyngitis	8 (8.7)	8 (8.8)	15 (22.1)	5 (6.8)	24 (11.0)
	Intraocular pressure increased	1 (1.1)	6 (6.6)	4 (5.9)	10 (13.5)	34 (15.6)
	Hypertension	15 (16.3)	10 (11.0)	6 (8.8)	7 (9.5)	24 (11.0)

Number of subjects with events (Incidence %)
a) The GALILEO study
b) The COPERNICUS study
c) Pooled data from the COPERNICUS and GALILEO studies
d) Defined as adverse events with an incidence of ≥10% in any group

Table 8. Major adverse events related to VEGF inhibition reported by Week 52 (safety analysis set)

		BRVO (VIBRANT study)		CRVO (GALILEO and COPERNICUS studies)		
		Laser group	Aflibercept group	Sham group[a)]	Sham group[b)]	Aflibercept group[c)]
Number of subjects evaluated		92	91	68	74	218
All adverse events related to VEGF inhibition[d)]		41 (44.6)	37 (40.7)	23 (33.8)	43 (58.1)	103 (47.2)
Arterial thromboembolic events		2 (2.2)	0	1 (1.5)	1 (1.4)	4 (1.8)
Venous thromboembolic events		1 (1.1)	1 (1.1)	0	2 (2.7)	11 (5.0)
Major adverse events[e)]	Conjunctival haemorrhage	15 (16.3)	22 (24.2)	3 (4.4)	15 (20.3)	32 (14.7)
	Retinal haemorrhage	2 (2.2)	4 (4.4)	9 (13.2)	10 (13.5)	28 (12.8)
	Vitreous haemorrhage	3 (3.3)	1 (1.1)	2 (2.9)	9 (12.2)	9 (4.1)
	Blood pressure increased	5 (5.4)	4 (4.4)	0	3 (4.1)	2 (0.9)
	Hypertension	15 (16.3)	10 (11.0)	6 (8.8)	7 (9.5)	24 (11.0)
	Protein urine present	1 (1.1)	0	1 (1.5)	5 (6.8)	4 (1.8)
	Urine protein/creatinine ratio increased	0	0	0	4 (5.4)	6 (2.8)

Number of subjects with events (Incidence %)
a) The GALILEO study
b) The COPERNICUS study
c) Pooled data from the COPERNICUS and GALILEO studies
d) Adverse events of "cardiomyopathy," "arterial thromboembolism," "venous thromboembolism," "gastrointestinal perforation and fistula," "haemorrhage," "hypertension," "leukoencephalopathy," "proteinuria," and "wound" are evaluated.
e) Defined as adverse events with an incidence of ≥5% in any group.

2.(ii).B.(4).2) Safety of aflibercept in combination with laser photocoagulation

Since macular laser photocoagulation was allowed as a rescue therapy and peripheral scatter laser photocoagulation was allowed for patients complicated by clinically relevant intraocular

neovascularization[7)] in the VIBRANT study, PMDA asked the applicant to explain the safety of aflibercept in combination with laser photocoagulation.

The applicant's explanation:

In the VIBRANT study, macular laser photocoagulation was allowed for patients in the aflibercept group as a rescue therapy, and aflibercept injection for patients in the laser group.[5)] Table 9 shows the incidence of adverse events during the period in which concomitant treatment with aflibercept and macular laser photocoagulation was allowed (from Week 36 onward in the aflibercept group, from Week 24 onward in the laser group). In the aflibercept group, the incidence of adverse events tended to be higher in patients "with concomitant macular laser photocoagulation" than in those "without concomitant macular laser photocoagulation," probably because the limited number of subjects "with concomitant macular laser photocoagulation" were evaluated in the aflibercept group. Intraocular pressure increased in the contralateral eye (2 of 9 subjects, 22.2%) was the only adverse event reported by more than 1 subject who received aflibercept "with concomitant macular laser photocoagulation." Adverse events attributed to the concomitant use of macular laser photocoagulation were not reported. In the laser group, the incidence of adverse events did not tend to differ between patients who were receiving concomitant aflibercept treatment and patients who were not.

Table 9. Adverse events reported by subjects after receiving concomitant treatment with aflibercept and macular laser photocoagulation
(VIBRANT study, safety analysis set, subjects who completed 24 weeks of treatment)

Treatment group	Aflibercept group[a)]		Laser group[b)]	
	With laser therapy	Without laser therapy	With aflibercept therapy	Without aflibercept therapy
Number of subjects evaluated	9	76	67	16
All adverse events	7 (77.8)	33 (43.4)	51 (76.1)	11 (68.8)
Adverse events in the study eye	4 (44.4)	13 (17.1)	29 (43.3)	6 (37.5)
Adverse events in the contralateral eye	3 (33.3)	8 (10.5)	9 (13.4)	3 (18.8)
Non-ocular adverse events	4 (44.4)	20 (26.3)	38 (56.7)	7 (43.8)
Death	0	0	0	0
Serious adverse events excluding death	2 (22.2)	2 (2.6)	3 (4.5)	0
Adverse events leading to treatment discontinuation	0	0	0	0
Adverse events related to the study drug	0	1 (1.3)	2 (3.0)	0
Adverse events related to the injection procedure	1 (11.1)	6 (7.9)	12 (17.9)	3 (18.8)

Number of subjects with events (Incidence %)
a) Adverse events reported during the period from Week 36 to Week 52
b) Adverse events reported during the period from Week 24 to Week 52

Moreover, in the VIBRANT study, subjects who experienced clinically relevant intraocular neovascularization[7)] were allowed to receive peripheral scatter laser photocoagulation at any time during the study, and 4 subjects in the laser group[18)] actually received such treatment. Of these 4 subjects, 3 received aflibercept concomitantly as rescue therapy and experienced events including retinal neovascularization and conjunctival haemorrhage after receiving aflibercept, but the severity was mild or moderate for all of them.

Based on the above, concomitant use of aflibercept with laser photocoagulation is unlikely to cause clinically relevant problems.

PMDA's view:

No substantial difference was seen between CRVO and BRVO patients in the incidence or type of adverse events associated with aflibercept, and no apparently greater risk was suggested in BRVO patients than in CRVO patients. In addition, although the number of patients studied was limited, concomitant use of aflibercept with laser photocoagulation did not tend to increase the incidence of adverse events in the clinical study possibly attributable to the treatment. Thus, presently neither aflibercept monotherapy nor concomitant therapy of aflibercept with laser photocoagulation in BRVO patients is likely to cause any particular safety issues. However, information should be provided

[18)] Of the 4 subjects, 1 subject received peripheral scatter laser photocoagulation and 3 subjects received panretinal laser photocoagulation.

promptly and appropriately to healthcare professionals in the clinical setting if new information on adverse events attributable to concomitant use of aflibercept with panretinal laser photocoagulation becomes available through the ongoing post-marketing surveillance covering patients with macular edema secondary to CRVO.

2.(ii).B.(5) Dosage and administration

PMDA asked the applicant to explain the appropriateness of the proposed dosage and administration for aflibercept.

The applicant's explanation:

Taking account of the following facts, aflibercept 2 mg was to be administered in the VIBRANT study once every 4 weeks from the start of treatment through Week 20, followed by once every 8 weeks thereafter:

- Because patients with macular edema secondary to RVO experience a rapid increase in intraocular VEGF levels early after disease onset, intraocular VEGF activity should be inhibited during the early phase of treatment.

- The phase III studies in patients with macular edema secondary to CRVO (the GALILEO[3)] and COPERNICUS[17)] studies), in which aflibercept 2 mg was to be administered once every 4 weeks from the start of treatment through Week 20, followed by as-needed treatment, have demonstrated the efficacy and safety of aflibercept.

- At the time of designing the study, a well-planned treatment given before deterioration of visual acuity was widely considered by healthcare professionals in the clinical setting to achieve better visual acuity than readministering after deterioration (Oubraham H et al. *Retina.* 2011;31:26-30, Gupta OP et al. *Ophthalmology.* 2010;1170:2134-2140).

- VEGF plays an important role in deteriorating visual acuity after development of macular edema in both wet AMD and macular edema secondary to RVO, and the efficacy of aflibercept 2 mg was demonstrated by studies in patients with wet AMD and in patients with CRVO with no particular safety issues. Therefore, the dose of aflibercept 2 mg was selected.

As a result, the VIBRANT study showed that the BCVA score in the aflibercept group improved rapidly during the initial phase of treatment and was largely maintained thereafter (Figure 1). In the VIBRANT study, the proportion of subjects in the aflibercept group who gained ≥10 letters in BCVA score from baseline during the initial phase of treatment (Weeks 4, 8, or 12) was 67.0% (61 of 91 patients). Table 10 shows BCVA scores in these subjects after initial treatment by time point at which "sustained visual improvement"[19)] was confirmed. There was no substantial difference in the change in BCVA score from baseline between at Week 24 and at the time point at which "sustained visual improvement"[19)] was confirmed, despite the variability among subjects in the time point. Thus, the number of additional aflibercept injections needed to stably maintain the rapidly improved visual acuity after the initial treatment was considered to vary among patients.

19) "Sustained visual improvement" was defined as "a gain of ≥10 letters in BCVA score from baseline sustained for 3 consecutive months of evaluation with the changes in BCVA score from baseline of the first and third months maintained within ±30% difference from that of the second month."

Table 10. BCVA scores in subjects in the aflibercept group who gained ≥10 letters in BCVA score from baseline during the initial phase of treatment, by time point sustained visual improvement was confirmed (VIBRANT study, FAS)

Time point sustained improvement confirmed after BCVA score improved ≥10 letters		Week 8	Week 12	Week 16	Week 20	Week 24	Sustained visual improvement not confirmed
Percentage (number of subjects concerned/number of subjects evaluated)		31.1 (19/61)	24.6 (15/61)	16.4 (10/61)	11.5 (7/61)	4.9 (3/61)	11.5 (7/61)
BCVA score	Baseline	54.5 ± 10.8	54.6 ± 13.1	61.4 ± 8.4	54.9 ± 9.6	59.7 ± 11.7	56.4 ± 14.4
	Time point sustained improvement confirmed[a)]	76.8 ± 6.0	75.5 ± 8.2	77.9 ± 4.5	77.0 ± 8.0	77.0 ± 14.1	-
	Week 24	81.7 ± 6.9	77.1 ± 8.5	80.8 ± 6.2	77.0 ± 6.8	79.0 ± 17.1	63.1 ± 20.1
Change in BCVA score from baseline	Time point of achievement[a)]	22.4 ± 9.2	20.9 ± 9.1	16.5 ± 6.9	22.1 ± 7.2	17.3 ± 6.5	-
	Week 24	27.2 ± 13.0	22.5 ± 9.7	19.4 ± 7.3	22.1 ± 7.0	19.3 ± 10.0	6.7 ± 9.7

Mean ± SD

a) Score at the middle month of 3 consecutive months in which sustained improvement was confirmed

Since the data from the phase III studies in patients with macular edema secondary to CRVO (the GALILEO[3)] and COPERNICUS[17)] studies) also showed variability among subjects in the time point at which sustained visual improvement was confirmed, proposed descriptions of the Dosage and Administration and Precautions for Dosage and Administration sections[20)] have been finally developed based on these data.

The same dose regimen as that for CRVO patients should be recommended for patients with macular edema secondary to BRVO, given the following facts:

- Although RVO is classified mainly into BRVO and CRVO based on the site of retinal vein occlusion, both disease subtypes have the same pathogenesis in which retinal ischemia and hypoxic conditions caused by turbulent or occluded retinal blood flow lead to VEGF production although expression levels are different (Funk M et al. *Invest Ophthalmol Vis Sci.* 2009;50:1025-1032) and the overexpressed VEGF increases vascular permeability leading to macular edema. In both disease subtypes, disease activity appears to be highest early after disease onset, and treatment is started immediately after diagnosis in routine clinical practice.

- The VIBRANT study and phase III studies in patients with macular edema secondary to CRVO (the GALILEO[3)] and COPERNICUS[17)] studies) revealed no substantial difference in the time to onset of clinical response. Specifically, the time to the first gain of ≥15 letters in BCVA score from baseline was 28 days in 25% of both all BRVO and all CRVO subjects, and 89 and 63 days in 50% of all BRVO and all CRVO subjects, respectively.

- Table 11 shows the relationship between the number of aflibercept injections and the efficacy after the initial treatment in which aflibercept was injected once every 4 weeks (6 doses in total) and the relationship did not tend to differ between BRVO and CRVO patients.

[20)] The precautions for patients with macular edema secondary to central retinal vein occlusion is described as follows:(1) Visual acuity should be measured approximately once a month, the results and the conditions of patients should be continuously monitored, and the need for treatment with aflibercept should be decided carefully. (2) Aflibercept is recommended to be administered once a month from the start of treatment until stable visual acuity has been achieved.

Table 11. Subgroup analysis of the efficacy by number of aflibercept injections from Week 24 to Week 52 (FAS)

Number of aflibercept injections[a)]	Time point	Proportion of subjects who gained ≥15 letters of visual acuity [b)]		Change in BCVA score from baseline[c)]		Change in CRT from baseline[c)]	
		BRVO[d)]	CRVO[e)]	BRVO[d)]	CRVO[e)]	BRVO[d)]	CRVO[e)]
0-1	Week 24	-	60.8 (31/51)	-	17.5 ± 10.4	-	-358.2 ± 195.6
	Week 52	-	70.6 (36/51)	-	16.2 ± 17.8	-	-329.2 ± 168.1
2-3	Week 24	72.7 (8/11)	63.6 (56/88)	23.2 ± 14.6	19.5 ± 14.0	-351.9 ± 247.4	-518.0 ± 215.3
	Week 52	72.7 (8/11)	61.4 (54/88)	20.7 ± 16.6	18.5 ± 15.8	-352.6 ± 279.4	-478.2 ± 259.5
≥4	Week 24	43.5 (27/62)	61.0 (36/59)	15.0 ± 11.0	17.4 ± 11.2	-281.9 ± 162.2	-480.7 ± 280.9
	Week 52	48.4 (30/62)	50.8 (30/59)	15.5 ± 12.6	16.7 ± 13.4	-286.4 ± 159.5	-440.6 ± 275.5

Subjects who completed 52 weeks of treatment were evaluated.
Missing values were imputed by using the LOCF method.
a) Number of aflibercept injections after the initial treatment in which aflibercept was injected once every 4 weeks (6 doses in total) through Week 52.
b) Percentage (number of subjects who experienced improvement/number of subjects evaluated)
c) Mean ± SD
d) VIBRANT study
e) Pooled data from the COPERNICUS and GALILEO studies

PMDA's view:
In the VIBRANT study, aflibercept was to be initially administered once every 4 weeks, 6 doses in total, and then administered once every 8 weeks, 4 doses in total. However, it was suggested that efficacy was expected in some patients even if they received <6 doses of aflibercept during the initial treatment. In addition, since the time to achievement of stable visual acuity varied from patient to patient, the number of aflibercept injections needed to achieve stable visual acuity may vary accordingly, as is the case with macular edema secondary to CRVO. Furthermore, an evaluation of the efficacy after achievement of stable visual acuity revealed that, the efficacy tended to wane in patients who received ≥4 doses in the VIBRANT study compared with patients in the phase III studies (the GALILEO[3)] and COPERNICUS[17)] studies) with macular edema secondary to CRVO. However, efficacy was still sustained with no substantially different tendency between BRVO and CRVO patients in relation between the efficacy and the time to onset of aflibercept action or the number of aflibercept injections. Although the site of retinal vein occlusion differs between BRVO and CRVO, the two disease subtypes have the same pathogenesis in which overexpressed VEGF increases vascular permeability leading to macular edema. Therefore, as is the case with macular edema secondary to CRVO, there is no major problem in determining whether administration of aflibercept is appropriate or not for individual patients by assessing the efficacy based on visual acuity etc., taking account of disease activity and control status of macular edema. Based on the above, in addition to including the minimum dosing interval required into the description of dosage and administration, it is appropriate to include statements that administration of aflibercept should be determined for individual patients based on visual acuity etc., and that once-every-4-week dosing is recommended until stable visual acuity has been achieved, as is the case with macular edema secondary to CRVO.

2.(ii).B.(6) Post-marketing investigations

The applicant's explanation:
An evaluation of the safety of aflibercept in patients with macular edema secondary to BRVO revealed neither a characteristic trend toward a higher incidence of adverse events than in patients with CRVO nor characteristic background factors of patients with BRVO that could affect the efficacy of aflibercept. Thus, a post-marketing surveillance covering patients with macular edema secondary to BRVO is considered unnecessary. After the market launch, efforts will be made to collect adverse event information from spontaneous reports, literature and academic sources, then to assess and review the information, and if any concerns arise about BRVO-specific safety issues, adequate safety measures will be taken appropriately.

PMDA's view:
Based on the comparison of study results from the additionally conducted clinical study and the clinical studies previously conducted in patients with macular edema secondary to CRVO, no particular problems with the use of aflibercept in BRVO patients and no new safety concerns have been identified in patients with macular edema secondary to BRVO receiving aflibercept. Therefore, neither additional

pharmacovigilance activity nor risk minimization action needs to be conducted in BRVO patients at present. The above issues will be finalized, based on comments raised in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the Application and Conclusion by PMDA

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

The assessment is ongoing. The results and PMDA's conclusion are to be reported in the Review Report (2).

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

The assessment is ongoing. The results and PMDA's conclusion are to be reported in the Review Report (2).

IV. Overall Evaluation

Based on the submitted data, the efficacy of aflibercept in patients with macular edema secondary to branch retinal vein occlusion (BRVO) has been demonstrated and its safety is acceptable in view of its observed benefits. Aflibercept provides a new therapeutic option for patients with macular edema secondary to BRVO and it has clinical significance.

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

Review Report (2)

May 15, 2015

I. Product Submitted for Registration

[Brand name]	(a) Eylea Intravitreal Injection 40 mg/mL
	(b) Eylea Intravitreal Injection Kit 40 mg/mL
[Non-proprietary name]	Aflibercept (Genetical Recombination)
[Applicant]	Bayer Yakuhin, Ltd.
[Date of application]	August 28, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administration Rule No. 8/2008 dated December 25, 2008).

PMDA's conclusions described in the Review Report (1) were supported by the expert advisors at the Expert Discussion including the opinion that neither additional pharmacovigilance activity nor risk minimization action is required for the change in indication for aflibercept.

III. Results of Compliance Assessment Concerning the Data Submitted in the Application and Conclusion by PMDA

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

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the application. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the application (5.3.5.1.1). PMDA concluded that the clinical study as a whole was performed in compliance with GCP and there should be no problem with conducting a regulatory review based on the submitted application documents. PMDA notified the applicant (sponsor) of the following observed finding requiring improvement but not having a substantial impact on the overall review of the study.

(Finding requiring improvement)
Sponsor
- Improper description in the contract for partially outsourcing clinical trials administration

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the dosage and administration as shown below, with the following condition. Since the re-examination imposed on the product at the time of approval as a drug with a new active ingredient (the indication of age-related macular degeneration with subfoveal choroidal neovascularization) is ongoing (until September 27, 2020), the currently added indication will also be covered by the re-examination.

[Indication]	Age-related macular degeneration with subfoveal choroidal neovascularization Macular edema secondary to ~~central~~ retinal vein occlusion Choroidal neovascularization in pathologic myopia[1)] Diabetic macular edema[1)] (The struck-through denotes the text deleted in this application.)
[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 ~~central~~ retinal vein occlusion and choroidal neovascularization in pathologic myopia[1)] 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[1)] 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. (The struck-through denotes the text deleted in this application.)
[Condition for approval]	The applicant is required to develop and appropriately implement a risk management plan.