Report on the Deliberation Results

May 1, 2025

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

Brand Name	(1) Vabysmo Solution for Intravitreal Injection 120 mg/mL
	(2) Vabysmo Kit for Intravitreal Injection 120 mg/mL
Non-proprietary Name	Faricimab (Genetical Recombination) (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	(1) September 6, 2024
	(2) March 17, 2025

Results of Deliberation

In its meeting held on April 25, 2025, the First Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The re-examination period is 10 years.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

April 11, 2025
Pharmaceuticals and Medical Devices Agency

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

Brand Name	(1) Vabysmo Solution for Intravitreal Injection 120 mg/mL
	(2) Vabysmo Kit for Intravitreal Injection 120 mg/mL
Non-proprietary Name	Faricimab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	(1) September 6, 2024
	(2) March 17, 2025[1)]

Dosage Form/Strength

(1) Aqueous solution for injection: Each vial contains 28.8 mg Faricimab (Genetical Recombination) in 0.24 mL solution.

(2) Aqueous solution for injection: Each pre-filled syringe contains 21.0 mg Faricimab (Genetical Recombination) in 0.175 mL solution.

Application Classification Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 564 of 2023 [*R5 yaku*]; PSEHB/PED Notification No. 0327-15 dated March 27, 2023, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of choroidal neovascularization associated with angioid streaks, 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 condition.

1) Although a marketing application for faricimab under the categories of drugs with new indications, drugs with new dosages, and drugs in additional dosage forms was filed on September 6, 2024, Vabysmo Kit for Intravitreal Injection 120 mg/mL was approved in March 2025. Accordingly, the application for faricimab was resubmitted under the categories of drugs with new indications and drugs with new dosages.

Indications

Age-related macular degeneration with subfoveal choroidal neovascularization

Diabetic macular edema

Macular edema following retinal vein occlusion

Choroidal neovascularization associated with angioid streaks

(Underline denotes additions.)

Dosage and Administration

[Age-related macular degeneration with subfoveal choroidal neovascularization]

Faricimab (Genetical Recombination) at a dose of 6.0 mg (0.05 mL) should be administered by intravitreal injection every 4 weeks, usually for 4 consecutive doses (the loading phase). The number of injections should be reduced, as appropriate, according to symptoms. In the subsequent maintenance phase, intravitreal injections should be given, usually every 16 weeks. The dosing interval should be adjusted according to symptoms, but the minimum interval is 8 weeks.

[Diabetic macular edema]

Faricimab (Genetical Recombination) at a dose of 6.0 mg (0.05 mL) should be administered by intravitreal injection every 4 weeks, usually for 4 consecutive doses. The number of injections should be reduced, as appropriate, according to symptoms. Then, the dosing interval should be extended incrementally, usually to 16 weeks. The dosing interval should be adjusted according to symptoms, but the minimum interval is 4 weeks.

[Macular edema following retinal vein occlusion, and Choroidal neovascularization associated with angioid streaks]

Faricimab (Genetical Recombination) at a dose of 6.0 mg (0.05 mL) should be administered by intravitreal injection. The minimum dosing interval is 4 weeks.

(Underline denotes additions.)

Approval Condition

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

Attachment

Review Report (1)

February 25, 2025

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

Product Submitted for Approval

Brand Name	(1) Vabysmo Solution for Intravitreal Injection 120 mg/mL
	(2) Vabysmo Kit for Intravitreal Injection 120 mg/mL
Non-proprietary Name	Faricimab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	September 6, 2024

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(1) Aqueous solution for injection: Each vial contains 28.8 mg Faricimab (Genetical Recombination) in 0.24 mL solution.

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Proposed Indications

Age-related macular degeneration with subfoveal choroidal neovascularization
Diabetic macular edema
Macular edema following retinal vein occlusion
Neovascular angioid streaks

(Underline denotes additions.)

Proposed Dosage and Administration

[Age-related macular degeneration with subfoveal choroidal neovascularization]
Faricimab (Genetical Recombination) at a dose of 6.0 mg (0.05 mL) should be administered by intravitreal injection every 4 weeks, usually for 4 consecutive doses (the loading phase). The number of injections should be reduced, as appropriate, according to symptoms. In the subsequent maintenance phase, intravitreal injections should be given, usually every 16 weeks. The dosing interval should be adjusted according to symptoms, but the minimum interval is 8 weeks.

[Diabetic macular edema]
Faricimab (Genetical Recombination) at a dose of 6.0 mg (0.05 mL) should be administered by intravitreal injection every 4 weeks, usually for 4 consecutive doses. The number of injections should be reduced, as appropriate, according to symptoms. Then, the dosing interval should be extended incrementally, usually to 16 weeks. The dosing interval should be adjusted according to symptoms, but the minimum interval is 4 weeks.

[Macular edema following retinal vein occlusion, and Neovascular angioid streaks]
Faricimab (Genetical Recombination) at a dose of 6.0 mg (0.05 mL) should be administered by intravitreal injection. The minimum dosing interval is 4 weeks.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

Faricimab (Genetical Recombination) (hereinafter referred to as “faricimab”) is a recombinant humanized bispecific immunoglobulin G1 monoclonal antibody that binds to both vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2), which are involved in angiogenesis, vascular leakage, etc. In Japan, Vabysmo, i.e., faricimab solution for intravitreal injection, was approved for the indications of "age-related macular degeneration with subfoveal choroidal neovascularization" and "diabetic macular edema" in March 2022 and the indication of "macular edema following retinal vein occlusion" in March 2024.

Angioid streaks (AS) occur due to breaks in the Bruch's membrane caused by the degeneration of its elastic fibers and are characterized by pigmented whitish lines radiating outward from the optic disc (*Today's Therapy in Ophthalmology* [in Japanese], the 3rd edition. Igaku-Shoin; 2017. p529-32). Although the disease is often asymptomatic, when choroidal neovascularization (CNV) arising from a break in the Bruch's membrane extends to the macular region, it causes reduced visual acuity etc. (*Retina*. 2013; 33: 1300-14). Since published literature suggests that VEGF-A and Ang-2 drive CNV (*Eye*. 2021; 35: 1305-16), faricimab is expected to improve CNV associated with AS.

For the development of faricimab for CNV associated with AS, a clinical study began in [redacted] 20[redacted] in Japan. Claiming that the Japanese clinical study results have confirmed the efficacy and safety of faricimab in the treatment of CNV associated with AS, the applicant has now filed a partial change application for faricimab.

Outside Japan, faricimab has not been approved for the indication of CNV associated with AS in any country or region.

Faricimab received an orphan drug designation (Orphan Drug Designation No. 564 of 2023 [*R5 yaku*]; PSEHB/PED Notification No. 0327-15 dated March 27, 2023) with the intended indication of "neovascular angioid streaks."

2. Quality and Outline of the Review Conducted by PMDA

The present application is intended for a new indication and a new dosage. A marketing application for Vabysmo Kit for Intravitreal Injection 120 mg/mL under the category of drugs in additional dosage forms has also been filed, and “Data Relating to Quality” have been submitted. Since the marketing application under the category of drugs in additional dosage forms has been reviewed prior to the present application, the outline of review for an additional dosage form is omitted from this report.

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. The non-clinical pharmacology data were previously evaluated for the initial approval of faricimab, and thus no new study data have been submitted.

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

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 faricimab, and thus no new study data have been submitted.

5. Toxicology and Outline of the Review Conducted by PMDA

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

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

The present application is intended for a new indication and a new dosage. Given that the product is a locally administered intravitreal formulation, and that no notable differences in the pharmacokinetics or pharmacodynamics of faricimab were observed among the currently approved indications, no data regarding biopharmaceutic studies and associated analytical methods and clinical pharmacology have been submitted.

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 a Japanese study presented in Table 1.

Table 1. Listing of efficacy and safety clinical study

Data category	Geographical location	Study ID CTD	Phase	Study population	No. of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Japan	JR44390 5.3.5.2-1	III	Patients with CNV associated with AS	24	6 mg faricimab intravitreal injections Q4W up to Week 8 From Week 12 onwards, 6 mg faricimab intravitreal injection if the dosing criteria were met.	Efficacy Safety

7.1 Japanese phase III study (CTD 5.3.5.2-1, Study JR44390 [ongoing since ■ 20■ (December 2024 data cutoff)])

An open-label, uncontrolled study was conducted in Japan to evaluate the efficacy and safety of faricimab in patients with CNV associated with AS[2)] (target sample size, 23 subjects[3)]). The primary analysis was performed when all enrolled subjects completed the assessment at Week 12 or withdrawal, and an interim analysis was performed when all enrolled subjects completed the assessment at Week 48 or withdrawal.

2) Patients with CNV associated with AS aged ≥18 years were eligible if the following key ocular inclusion criteria (the study eye) were met.
- A subfoveal component related to CNV activity identified by FA or OCT
- Active CNV confirmed by FA and/or CNV exudation confirmed on OCT
- BCVA of 78-24 letters using the ETDRS VA test assessed at a starting distance of 4 m on Day 1

3) For the primary endpoint of BCVA change from baseline at Week 12, a target sample size of 23 subjects would provide 80% power under the following assumptions: an expected improvement of 5 letters with faricimab, 1 dropout, a threshold of 0 letters, a standard deviation of 9 letters, and a one-sided significance level of 5%.

Faricimab 6 mg was to be administered by intravitreal injection into the study eye every 4 weeks (Q4W) for a total of 3 doses. From Week 12 onwards, faricimab 6 mg was to be administered by intravitreal injection if the dosing criteria[4] were met.

All of 24 enrolled subjects received the study drug and were included in the efficacy and safety populations. There were no study treatment discontinuations through Week 48.

Table 2 shows the results of the primary endpoint of the change from baseline in best corrected visual acuity (BCVA) at Week 12 as measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart.[5] The lower limit of the 90% confidence interval (CI) was above the pre-specified threshold of 0 letters. Figure 1 shows BCVA change from baseline through Week 48.

Table 2. BCVA change from baseline at Week 12 (letters) (Study JR44390, Efficacy population, MMRM)

Baseline BCVA[a)]	BCVA at Week 12[a)]	BCVA change from baseline at Week 12[b), c)]
55.5 ± 16.5 (24)	61.2 ± 16.7 (24)	5.8 [3.0, 8.5]

a) Mean ± SD (No. of evaluable subjects), b) Least-squares mean [90% CI]
c) Calculated using a mixed-effect model for repeated measures (MMRM) with the changes from baseline at Weeks 4-12 as response variables and visit and baseline BCVA as fixed effects. The MMRM assumed an unstructured covariance matrix.

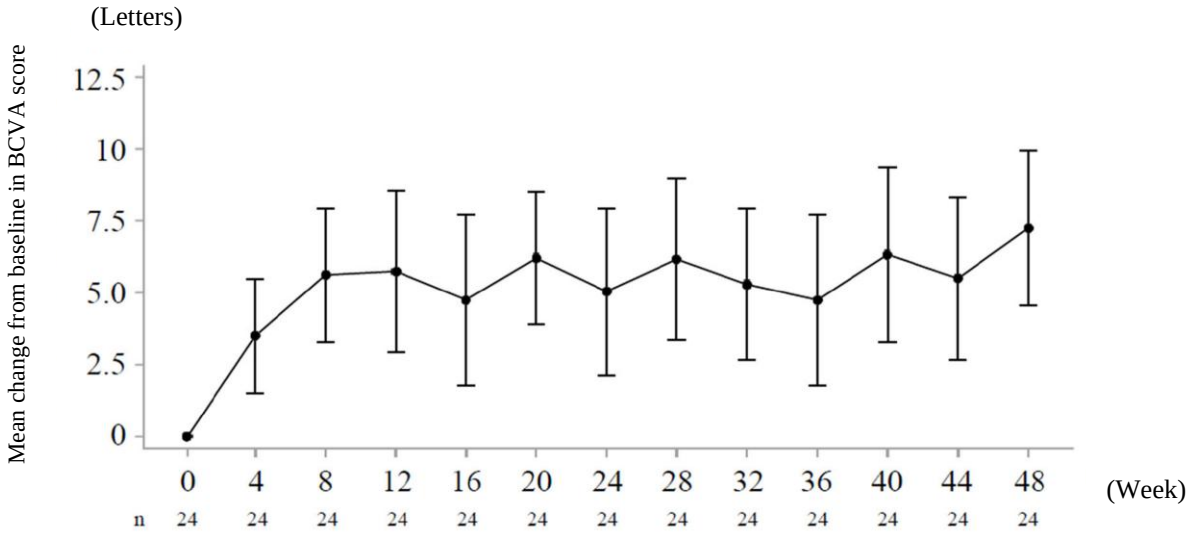

Figure 1. BCVA change from baseline through Week 48 (letters)
(Study JR44390, LS mean ± 90% CI based on analytical method similar to the primary analysis, Efficacy population, MMRM)

The incidences of adverse events in the study eye and non-ocular adverse events through Week 48 were 41.7% (10 of 24 subjects) and 66.7% (16 of 24 subjects), respectively. No deaths were reported. No serious adverse events occurred in the study eye. The incidence of non-ocular serious adverse events was 8.3% (2 of 24 subjects

4) If any of the following findings indicative of CNV activity in AS were observed based on the judgment of the investigator, or multiple consecutive injections were deemed necessary by the investigator.
- A loss of ≥5 BCVA letters since the previous study visit
- New or persisting subretinal fluid or intraretinal fluid
- New or persisting macular hemorrhage

5) Handling of intercurrent events for the primary endpoint is as follows:
- The use of prohibited therapy in the study eye and study treatment discontinuation were considered intercurrent events. Treatment policy strategy was to be used to address these intercurrent events, and observations after the use of prohibited therapy or study treatment discontinuation were also to be used for analyses.

[acute cholecystitis; and diverticulitis (1 subject each)]), and both events were assessed as causally unrelated to study drug. There were no adverse events in the study eye or non-ocular adverse events assessed as causally related to study drug through Week 48.

7.R Outline of the review conducted by PMDA

7.R.1 Strategy for efficacy evaluation of faricimab

7.R.1.1 Design of Japanese phase III study

The applicant's explanation about the reasons for designing and conducting a Japanese phase III study in patients with CNV associated with AS (Study JR44390) as an open-label, uncontrolled study:

In addition to the following viewpoints (1) and (2), the applicant considered that even an open-label uncontrolled study can evaluate the efficacy of faricimab [see Section 7.R.1.2]. Thus, the applicant decided to design Study JR44390 as an open-label, uncontrolled study in Japan.

(1) Feasibility of a global study

The conduct of a global study was considered difficult because there is no plan for the development of faricimab for patients with CNV associated with AS overseas[6)] for the following reasons.

- In Europe, the major Asian countries/regions (Korea, China, Hong Kong, Singapore, Thailand, and Taiwan), Australia, and New Zealand, a VEGF inhibitor, Ranibizumab (Genetical Recombination) (hereinafter referred to as "ranibizumab") has been approved for the indication of visual impairment due to CNV and can be used also in the treatment of CNV associated with AS.
- In the US, VEGF inhibitors have not been approved for the indication of CNV associated with AS, but are eligible for reimbursement.

(2) Feasibility of a controlled study

Patients with AS who develop CNV in the macular region have a poor prognosis for visual acuity if left untreated, and early treatment initiation is important to prevent irreversible visual dysfunction (*Retina*. 2019; 39: 1-11). Thus, not initiating early treatment is inappropriate. Although treatment with intravitreal VEGF inhibitors in patients with CNV associated with AS has been shown to improve or stabilize visual acuity and central retinal thickness (*Retina*. 2013; 33: 1300-14), no VEGF inhibitors have been approved for the indication of CNV associated with AS in Japan. Other existing therapies such as retinal laser photocoagulation and photodynamic therapy (PDT) have poor outcomes, e.g., little effect in maintaining visual acuity and a high recurrence rate of CNV (*Retina*. 2019; 39: 1-11). Based on the above, the conduct of a controlled study with an appropriate control group, including a sham procedure group (in which a needleless syringe is pressed against the conjunctival surface), was considered difficult.

PMDA's view:

Given that no controlled studies etc. have evaluated the efficacy and safety of faricimab in patients with CNV associated with AS, essentially, it is desirable to conduct a controlled study with an appropriate control group and obtain robust data concerning the efficacy and safety of faricimab in patients with CNV associated with

6) F. Hoffmann-La Roche has rights to develop faricimab overseas.

AS. However, the above explanation provided by the applicant in the subsections (1) and (2) is understandable, and taking also account of discussion etc. in Section 7.R.1.2, designing and conducting Study JR44390 as an open-label, uncontrolled study is acceptable.

7.R.1.2 Appropriateness of efficacy evaluation plan for Japanese phase III study

The applicant's explanation about the appropriateness of efficacy evaluation plan for Study JR44390:

The primary endpoint for Study JR44390, i.e., BCVA change from baseline, has been established as an efficacy outcome measure in macular disease trials, and open-label clinical studies of ranibizumab[7)] did not tend to overestimate BCVA changes. Given these points, the applicant considered that even an open-label, uncontrolled study could evaluate the efficacy of faricimab. Thus, the change from baseline in BCVA was chosen. Week 12 was selected as the timing for assessment of the primary endpoint because the following results with VEGF inhibitors predicted that an improvement in visual acuity with faricimab could be detected at Week 12.

- In the MINERVA study, the change from baseline in BCVA plateaued at 3 months after initiation of ranibizumab treatment, and this gain in BCVA was sustained thereafter (*Retina*. 2018; 38: 1464-77).
- In a prospective study in which patients with CNV secondary to AS received Aflibercept (Genetical Recombination) (hereinafter referred to as "aflibercept"), an improvement in BCVA was observed at Week 12 (*Graefes Arch Clin Exp Ophthalmol*. 2020; 258: 311-8).

Based on the considerations described below, the following efficacy evaluation plan was employed for Study JR44390:

The efficacy of faricimab was to be declared if the lower limit of the 90% CI for the primary endpoint of the change from baseline in BCVA at Week 12 as measured using the ETDRS chart was above the pre-specified threshold of 0 letters.

- Since a global phase III study in patients with neovascular age-related macular degeneration (nAMD) (Study GR40306) demonstrated the non-inferiority of faricimab to aflibercept in the change from baseline in BCVA, its efficacy is expected also in patients with CNV associated with AS, i.e., the patient population of Study JR44390. On the other hand, given the natural history of visual acuity in the subgroup of patients with CNV associated with AS in the sham group of the MINERVA study, an improvement in visual acuity is not expected if left untreated. Thus, a clinically meaningful minimum improvement of 0 letters was proposed as an efficacy threshold.
- According to sample size determination at the time of designing the study, 28 subjects were required to provide 80% power at a two-sided significance level of 5%, assuming an expected improvement from baseline in BCVA of 5 letters[8)] with faricimab and a threshold of 0 letters. Given that AS is a rare disease, and that the number of Japanese patients is limited, it was considered difficult to enroll the required number

7) A randomized, double-masked, sham-controlled study in patients with CNV associated with causes other than nAMD and pathologic myopia, including those with AS (MINERVA study) (*Retina*. 2018; 38: 1464-77), and Japanese open-label, uncontrolled studies in patients with nAMD, branch retinal vein occlusion, or central retinal vein occlusion (Studies 1201 and E2301).

8) The mean BCVA change from baseline at Week 12 was 6.7 letters in the faricimab group of faricimab phase III studies in treatment-naïve patients with nAMD (Studies GR40306 and GR40844) (the 2 studies combined), and a lower improvement in BCVA was expected in the present study enrolling also patients previously treated with VEGF inhibitors, compared with Studies GR40306 and GR40844. Taking account of these findings, an improvement of 5 letters was assumed.

of subjects. Thus, referring to the ICH E9 guideline, the use of the lower limit of the 90% CI for efficacy assessment was decided.

PMDA's view:
The applicant's explanation is acceptable.

However, as the long-term prognosis for visual acuity is also important for AS patients, efficacy at Week 48 should also be evaluated. The efficacy of faricimab will be discussed also in Section 7.R.2.

7.R.2 Efficacy

The applicant's explanation about the efficacy of faricimab in the treatment of CNV associated with AS based on the results of Study JR44390:
In the primary analysis of the primary endpoint, the lower limit of the 90% CI for the change from baseline in BCVA at Week 12 was above the pre-specified efficacy threshold of 0 letters, meeting the pre-specified success criterion for the study (Table 2). The lower limit of the 95% CI was 2.4 letters. The BCVA gained up to Week 12 was sustained until Week 48 (Figure 1).

Table 3 shows the results of key secondary endpoints.

Table 3. Results of key secondary endpoints (Study JR44390, Efficacy population)

	Baseline[a)]	Week 12	Week 48
No. of evaluable subjects	24	24	24
Visual endpoints			
Proportion of patients who gained ≥15 letters in BCVA from baseline	—	12.5 (3/24) [2.7, 32.4]	20.8 (5/24) [7.1, 42.2]
Proportion of patients who avoided loss of ≥15 letters in BCVA from baseline	—	100 (24/24) [85.8, 100]	100 (24/24) [85.8, 100]
Anatomical endpoints using OCT			
CST[b)] (μm)	334.6 ± 111.6	228.2 ± 48.8 −106.4 [−126.9, −85.9]	230.8 ± 56.3 −103.8 [−126.5, −81.1]
Proportion of patients with absence of intraretinal fluid[c)]	29.2 (7/24) [12.6, 51.1]	70.8 (17/24) [48.9, 87.4]	66.7 (16/24) [44.7, 84.4]
Proportion of patients with absence of subretinal fluid[d)]	58.3 (14/24) [36.6, 77.9]	95.8 (23/24) [78.9, 99.9]	87.5 (21/24) [67.6, 97.3]
Proportion of patients with absence of intraretinal fluid[c)] and subretinal fluid[d)]	8.3 (2/24) [1.0, 27.0]	66.7 (16/24) [44.7, 84.4]	58.3 (14/24) [36.6, 77.9]

Missing data were not imputed.
Proportion Upper row, % (Number of subjects in category/Number of evaluable subjects); Lower row, 95% CI. CI was calculated using the Clopper-Pearson method.
Continuous variables Upper row, Values at Week 12 or 48 (Mean ± SD); Lower row, LS mean change from baseline [95% CI]. MMRM (an unstructured covariance structure within subjects) analysis with visit and baseline value as covariates.
—, Not applicable
a) Mean ± SD
b) Central subfield thickness (CST) was defined as the distance between internal limiting membrane and Bruch's membrane in the 1 mm diameter area centered on the fovea.
c) Intraretinal fluid was defined as intraretinal effusion and intraretinal cysts in the 1 mm diameter area centered on the fovea.
d) Subretinal fluid was defined as subretinal effusion in the 1 mm diameter area centered on the fovea.

Table 4 shows the results of the primary endpoint of the BCVA change from baseline at Week 12 by baseline characteristics. In the subgroup of patients aged ≥75 years, 2 of 3 subjects had a loss in BCVA from baseline (−1 letter and −5 letters at Week 12, respectively). Even at the late stage in the therapeutic course of a VEGF

inhibitor, patients with CNV secondary to nAMD remain at risk for visual decline due to prolonged disease duration (*Ophthalmology*. 2013; 120: 2292-9). It has been reported that patients with CNV associated with AS who had been pretreated with VEGF inhibitors experienced less improvement in visual acuity than treatment-naïve patients (*Graefes Arch Clin Exp Ophthalmol*. 2020; 258: 311-8). In the 2 subjects with a loss in BCVA from baseline, the number of months since diagnosis of AS and the number of VEGF inhibitor injections at baseline were 156 months and 61 injections, respectively, and 51 months and 13 injections, respectively. These patients were considered unlikely to achieve an improvement in BCVA. In these 2 subjects, the BCVA changes from baseline at Week 48 were −1 letter and 0 letters, respectively. Although evaluation was difficult due to the small number of subjects in some categories of baseline characteristics, none of the baseline characteristics clearly affected the efficacy of faricimab.

Table 4. BCVA Change from baseline at Week 12 (letters) by baseline characteristics (Study JR44390, Efficacy population)

Baseline characteristics		Baseline[a)]	Week 12[b)]
Overall population		55.5 ± 16.5 (24)	61.2 ± 16.7 (24) 5.8 [2.4, 9.1]
Baseline BCVA[c)]	55-73 letters	67.7 ± 5.9 (12)	70.3 ± 8.9 (12) 2.6 [−1.6, 6.8]
	≤54 letters	40.4 ± 11.0 (11)	49.7 ± 16.8 (11) 9.4 [3.8, 14.9]
CNV subtype[d)]	Predominantly Classic Type	54.1 ± 17.0 (15)	59.6 ± 18.5 (15) 5.5 [0.9, 10.2]
	Occult Type	58.3 ± 17.4 (8)	63.9 ± 14.8 (8) 5.6 [−0.7, 12.0]
Total area of CNV lesion[e)]	1-3 mm^2	64.7 ± 6.7 (3)	73.0 ± 5.3 (3) 8.3 [5.3, 11.3]
	>3 mm^2	54.1 ± 17.2 (21)	59.5 ± 17.2 (21) 5.4 [1.6, 9.2]
Age	<75 years	55.5 ± 15.5 (21)	62.3 ± 15.8 (21) 6.8 [3.2, 10.4]
	≥75 years	55.0 ± 26.9 (3)	53.3 ± 24.6 (3) −1.7 [−6.3, 3.0]
Sex	Female	52.9 ± 18.9 (14)	58.0 ± 20.0 (14) 5.1 [1.1, 9.2]
	Male	59.1 ± 12.5 (10)	65.7 ± 9.8 (10) 6.6 [0.5, 12.7]
Previous treatment with VEGF inhibitor[f)]	Yes	52.4 ± 17.8 (17)	57.0 ± 17.6 (17) 4.6 [0.7, 8.6]
	No	63.0 ± 10.1 (7)	71.4 ± 8.7 (7) 8.4 [1.2, 15.7]
PXE diagnosis[g)]	Yes	60.4 ± 13.9 (9)	64.1 ± 17.5 (9) 3.7 [−2.2, 9.5]
	No	52.4 ± 16.5 (5)	57.6 ± 17.6 (5) 5.2 [−0.5, 10.9]

Analytical method and handling of intercurrent were the same as those used for the primary analysis of the primary endpoint.
a) Mean ± SD (No. of evaluable subjects)
b) Upper row, Mean ± SD (No. of evaluable subjects); Lower row, LS mean change from baseline [95% CI].
c) One subject with a baseline BCVA ≥74 letters was not included in the subgroup analysis by baseline characteristics.
d) CNV subtypes were classified by fluorescein angiography (FA) as classic type, defined as CNV located above the retinal pigment epithelium (RPE) and occult, defined as CNV located below the RPE. Among classic type lesions, those with classic CNV accounting for >50% of the total lesion area were defined as predominantly classic type. One subject with classic type lesion in which classic CNV accounted for ≤50% of the total lesion area was not included in the subgroup analysis by baseline characteristics.
e) CNV lesion was defined as areas of CNV and atrophy with hyperfluorescence in the early phase of the angiogram and areas of hemorrhage with hypofluorescence.
f) Bevacizumab, ranibizumab, aflibercept, or brolucizumab
g) Nine subjects without results of pseudoxanthoma elasticum (PXE) assessment and 1 subject with possible PXE were not included in the subgroup analysis by baseline characteristics.

PMDA's view:

Given the following results of Study JR44390, etc., the efficacy of faricimab in Japanese patients with CNV associated with AS was demonstrated.

- The lower limit of the 90% CI for the primary endpoint of the BCVA change from baseline at the primary time point of Week 12 was above the pre-specified threshold of 0 letters, meeting the pre-specified success criterion for the study, and this gain in BCVA was sustained until Week 48 (Figure 1). The results of secondary endpoints supported the results of the primary endpoint (Table 3).

7.R.3 Safety

The applicant's explanation about the safety profile of faricimab in patients with CNV associated with AS:

Table 5 shows the incidence of adverse events in the study eye in Study JR44390. There were no serious adverse events, adverse events leading to treatment discontinuation, or adverse events assessed as causally related to study drug. No adverse events occurred with a clearly higher incidence in patients with AS as compared with the results from clinical studies in patients with retinal vein occlusion (RVO), nAMD, or diabetic macular edema (DME).

Table 5. Incidence of adverse events in the study eye (Safety population)

	Study JR44390	Pooled RVO[a)]	Pooled nAMD[b)]	Pooled DME[c)]
	Week 48	Entire treatment period	Entire treatment period	Entire treatment period
No. of evaluable subjects	24	1250	704	1262
Total patient-years of exposure	22.21	1368.71	1425.61	2296.07
All adverse events	10 (41.7) 72.05	476 (38.1) 68.02	378 (53.7) 67.76	624 (49.4) 56.88
Serious adverse events	0 0	56 (4.5) 4.68	33 (4.7) 2.74	60 (4.8) 3.35
Adverse events leading to treatment discontinuation	0 0	12 (1.0) 0.88	17 (2.4) 1.19	17 (1.3) 0.83
Sight-threatening adverse events[d)]	0 0	40 (3.2) 3.07	27 (3.8) 2.10	58 (4.6) 3.05
Adverse events assessed as causally related to study drug	0 0	51 (4.1) 6.21	30 (4.3) 2.88	41 (3.2) 2.35
Serious adverse events assessed as causally related to study drug	0 0	6 (0.5) 0.66	10 (1.4) 0.70	7 (0.6) 0.39
All adverse events (Events observed in Study JR44390)				
Conjunctival haemorrhage	2 (8.3) 9.01	54 (4.3) 6.36	64 (9.1) 5.12	96 (7.6) 4.70
Dry eye	2 (8.3) 9.01	30 (2.4) 3.51	29 (4.1) 2.10	56 (4.4) 2.66
Intraocular pressure increased	1 (4.2) 13.51	57 (4.6) 9.79	29 (4.1) 3.30	53 (4.2) 3.48
Conjunctivitis	1 (4.2) 4.50	12 (1.0) 1.17	5 (0.7) 0.42	23 (1.8) 1.09
Visual acuity reduced	1 (4.2) 4.50	10 (0.8) 0.88	4 (0.6) 0.42	9 (0.7) 0.48
Iritis	1 (4.2) 13.51	8 (0.6) 0.80	10 (1.4) 0.91	5 (0.4) 0.22
Lacrimation increased	1 (4.2) 4.50	8 (0.6) 0.73	6 (0.9) 0.98	15 (1.2) 0.87
Conjunctivitis allergic	1 (4.2) 4.50	4 (0.3) 0.66	7 (1.0) 0.49	6 (0.5) 0.26
Swelling of eyelid	1 (4.2) 4.50	2 (0.2) 0.15	2 (0.3) 0.14	4 (0.3) 0.26
Blepharospasm	1 (4.2) 4.50	1 (<0.1) 0.15	— —	2 (0.2) 0.13

Upper row, Number of subjects with event (Incidence (%)); Lower row, Exposure-adjusted incidence rate (Events per 100 patient-years)

—: Event term is not listed, and "0" is not stated explicitly in the adverse event summary report.

a) Results of pooled analysis of adverse events occurring during the faricimab treatment period (the entire treatment period in the faricimab group and the period after the primary time point in the aflibercept group) from Studies GR41984 and GR41986

b) Results of pooled analysis of adverse events occurring in the faricimab group from Studies GR40306 and GR40844

c) Results of pooled analysis of adverse events occurring in the faricimab group from Studies GR40349 and GR40398

d) An adverse event that meets any of the following criteria:

- An adverse event resulting in a decrease of ≥30 letters in VA score (compared with the last assessment of VA prior to the most recent assessment) lasting for more than 1 hour.
- An adverse event requiring medical or surgical intervention to prevent permanent loss of sight.
- An adverse event with severe intraocular inflammation (i.e., endophthalmitis, 4+ anterior chamber cell, 4+ anterior chamber flare, or 4+ vitritis).

Table 6 shows the incidence of non-ocular adverse events in Study JR44390. Acute cholecystitis (4.2% [1 of 24 subjects]) and diverticulitis (4.2% [1 of 24 subjects]) which were classified as serious adverse events occurred, but their causal relationship to study drug was ruled out. There were no adverse events leading to treatment discontinuation. No adverse events occurred with a clearly higher incidence in patients with AS as compared with the results from clinical studies in patients with RVO, nAMD, or DME.

Table 6. Incidence of non-ocular adverse events (Safety population)

	Study JR44390	Pooled RVO[a)]	Pooled nAMD[b)]	Pooled DME[c)]
	Week 48	Entire treatment period	Entire treatment period	Entire treatment period
No. of evaluable subjects	24	1250	704	1262
Total patient-years of exposure	22.21	1368.71	1425.61	2296.07
All adverse events	16 (66.7) 216.15	705 (56.4) 140.94	519 (73.7) 141.69	929 (73.6) 172.42
Death	0 0	10 (0.8) 0.73	23 (3.3) 1.68	58 (4.6) 2.70
Serious adverse events other than death	2 (8.3) 9.01	142 (11.4) 15.64	133 (18.9) 14.94	310 (24.6) 25.13
Adverse events leading to treatment discontinuation	0 0	10 (0.8) 0.80	11 (1.6) 0.77	16 (1.3) 0.70
Adverse events assessed as causally related to study drug	0 0	12 (1.0) 1.83	5 (0.7) 0.42	9 (0.7) 0.39
Serious adverse events assessed as causally related to study drug	0 0	7 (0.6) 0.58	4 (0.6) 0.28	5 (0.4) 0.22
All adverse events (Events observed in Study JR44390)				
Nasopharyngitis	4 (16.7) 31.52	52 (4.2) 5.33	55 (7.8) 4.63	103 (8.2) 5.40
COVID-19	3 (12.5) 13.51	174 (13.9) 14.83	34 (4.8) 2.38	77 (6.1) 3.40
Arthralgia	3 (12.5) 13.51	25 (2.0) 2.05	40 (5.7) 3.30	39 (3.1) 1.79
Herpes zoster	2 (8.3) 13.51	12 (0.1) 0.88	12 (1.7) 0.84	16 (1.3) 0.7
Contusion	2 (8.3) 9.01	8 (0.6) 0.66	14 (2.0) 1.12	13 (1.0) 0.61
Hand dermatitis	2 (8.3) 4.50	— —	2 (0.3) 0.14	1 (<0.1) 0.09
Hypertension	1 (4.2) 4.50	74 (5.9) 7.31	43 (6.1) 3.16	103 (8.2) 5.05
Upper respiratory tract infection	1 (4.2) 4.50	35 (2.8) 4.53	24 (3.4) 2.10	34 (2.7) 1.87
Influenza	1 (4.2) 4.50	31 (2.5) 2.48	14 (2.0) 0.98	34 (2.7) 1.65
Bronchitis	1 (4.2) 9.01	18 (1.4) 1.68	24 (3.4) 1.75	41 (3.2) 1.83
Osteoarthritis	1 (4.2) 4.50	16 (1.3) 1.61	21 (3.0) 1.54	22 (1.7) 1.05
Pyrexia	1 (4.2) 4.50	12 (1.0) 1.17	11 (1.6) 0.84	19 (1.5) 1.00
Nausea	1 (4.2) 4.50	8 (0.6) 0.80	6 (0.9) 0.42	35 (2.8) 1.74
Blood pressure increased	1 (4.2) 4.50	8 (0.6) 0.88	5 (0.7) 0.35	9 (0.7) 0.39
Cholelithiasis	1 (4.2) 4.50	8 (0.6) 0.73	3 (0.4) 0.21	10 (0.8) 0.44
Oropharyngeal pain	1 (4.2) 4.50	5 (0.4) 0.44	4 (0.6) 0.35	11 (0.9) 0.57
Neuropathy peripheral	1 (4.2) 4.50	4 (0.3) 0.29	2 (0.3) 0.14	8 (0.6) 0.35
Rheumatoid arthritis	1 (4.2) 4.50	3 (0.2) 0.22	2 (0.3) 0.21	2 (0.2) 0.13
Ligament sprain	1 (4.2) 4.50	2 (0.2) 0.22	5 (0.7) 0.35	6 (0.5) 0.30
Hypoaesthesia	1 (4.2) 4.50	2 (0.2) 0.15	1 (0.1) 0.07	8 (0.6) 0.35
Dermatophytosis of nail	1 (4.2) 4.50	2 (0.2) 0.15	1 (0.1) 0.07	1 (<0.1) 0.04
Ankle fracture	1 (4.2) 4.50	1 (<0.1) 0.07	3 (0.4) 0.21	5 (0.4) 0.22
Dermal cyst	1 (4.2) 4.50	1 (<0.1) 0.07	2 (0.3) 0.14	4 (0.3) 0.17
Acute cholecystitis	1 (4.2) 4.50	1 (<0.1) 0.15	0 0	2 (0.2) 0.09
Post-acute COVID-19 syndrome	1 (4.2) 4.50	1 (<0.1) 0.07	— —	— —
Tinea cruris	1 (4.2) 4.50	1 (<0.1) 0.07	— —	— —
Hypertonic bladder	1 (4.2)	—[d)]	1 (0.1)	0

	Study JR44390	Pooled RVO[a)]	Pooled nAMD[b)]	Pooled DME[c)]
	Week 48	Entire treatment period	Entire treatment period	Entire treatment period
No. of evaluable subjects	24	1250	704	1262
Total patient-years of exposure	22.21	1368.71	1425.61	2296.07
	4.50	0.07	0.07	0
Diverticulitis	1 (4.2) 4.50	— —	4 (0.6) 0.35	1 (<0.1) 0.04
Anxiety disorder	1 (4.2) 4.50	— —	1 (0.1) 0.07	1 (<0.1) 0.04
Oropharyngeal discomfort	1 (4.2) 4.50	— —	1 (0.1) 0.14	— —
Ovarian cyst	1 (4.2) 4.50	— —	— —	2 (0.2) 0.09
Occipital neuralgia	1 (4.2) 4.50	— —	— —	— —
Erythroplasia	1 (4.2) 4.50	— —	— —	— —

Upper row, Number of subjects with event (Incidence (%)); Lower row, Exposure-adjusted incidence rate (Events per 100 patient-years)

—: Event term is not listed, and "0" is not stated explicitly in the adverse event summary report.

a) Results of pooled analysis of adverse events occurring during the faricimab treatment period (the entire treatment period in the faricimab group and the period after the primary time point in the aflibercept group) from Studies GR41984 and GR41986

b) Results of pooled analysis of adverse events occurring in the faricimab group from Studies GR40306 and GR40844

c) Results of pooled analysis of adverse events occurring in the faricimab group from Studies GR40349 and GR40398

d) No numerical values are available because first-onset adverse events occurring during the faricimab treatment period were counted. In the lower row, multiple occurrences of the event in an individual were counted as separate events.

In Study JR44390, among the important identified risks in the risk management plan (RMP) for faricimab, infectious endophthalmitis,[9)] rhegmatogenous retinal detachment/retinal tear,[10)] or retinal pigment epithelial tear[11)] was not reported. However, intraocular inflammation[12)] (4.2% [1 of 24 subjects]) (iritis) and increase in intraocular pressure[13)] (4.2% [1 of 24 subjects]) (intraocular pressure increased) occurred, both of which were mild in severity and non-serious, and their causal relationship to study drug was ruled out. As systemic adverse events related to VEGF inhibition[14)] including arterial thromboembolic events,[15)] which are categorized as important potential risks, contusion (8.3% [2 of 24 subjects]), blood pressure increased (4.2% [1 of 24 subjects]), and hypertension (4.2% [1 of 24 subjects]) occurred. All of these events were mild or moderate in severity and non-serious, and their causal relationship to study drug was ruled out.

Pseudoxanthoma elasticum (PXE) is a systemic disorder characterized by progressive degeneration and calcification of elastic fibers (*Jpn J Dermatol*. 2017; 127: 2447-54). More than half of patients with PXE have AS (*Retina*. 2019; 39: 1-11), and PXE is associated with an increased risk of ischemic heart disease, ischemic

9) MedDRA PTs "endophthalmitis," "candida endophthalmitis," "mycotic endophthalmitis," and "pseudoendophthalmitis"

10) MedDRA PTs "rhegmatogenous retinal detachment," "retinal detachment," and "retinal tear"

11) MedDRA PT "retinal pigment epithelial tear"

12) MedDRA PTs "anterior chamber inflammation," "chorioretinitis," "iridocyclitis," "iritis," "keratic precipitates," "keratouveitis," "post procedural inflammation," "uveitis," "vitritis," "vitreal cells," "non-infectious endophthalmitis," "anterior chamber flare," "eye inflammation," "ocular vasculitis," "retinal vasculitis," "cyclitis," "choroiditis," "noninfective chorioretinitis," "anterior chamber cell," "anterior chamber fibrin," "hypopyon," "retinitis," "toxic anterior segment syndrome," "viral keratouveitis," "viral uveitis," "vitreous abscess," "vitreous haze," "retinal occlusive vasculitis," and "haemorrhagic occlusive retinal vasculitis"

13) MedDRA PTs "intraocular pressure increased," "intraocular pressure fluctuation," "intraocular pressure test abnormal," and "ocular hypertension"

14) MedDRA SMQs "hypertension," "haemorrhages," "central nervous system haemorrhages and cerebrovascular conditions," "haemorrhagic central nervous system vascular conditions," "embolic and thrombotic events, arterial," "myocardial infarction," "other ischaemic heart disease," "ischaemic central nervous system vascular conditions," and "embolic and thrombotic events, venous"

15) MedDRA SMQs "embolic and thrombotic events, arterial," "myocardial infarction," "other ischaemic heart disease," and "ischaemic central nervous system vascular conditions"

cerebral infarction, etc. (*Retina*. 2019; 39: 1-11, *Jpn J Dermatol*. 2017; 127: 2447-54). Table 7 shows the incidence of adverse events by presence or absence of diagnosis of PXE.

In Study JR44390, no new safety concerns with faricimab were identified in subjects with PXE, and no increased risk of ischemic heart disease, ischemic cerebral infarction, etc., has been suggested following intravitreal injection of a VEGF inhibitor in PXE patients with CNV (*Retina*. 2016; 36: 483-91, *Am J Ophthalmol*. 2011; 152: 695-703).

Table 7. Incidence of adverse events by presence or absence of diagnosis of PXE (Study JR44390, Safety population)

	Overall	Diagnosis of PXE	
		Yes	No[a)]
No. of evaluable subjects	24	9	15
Adverse events in the study eye	10 (41.7)	4 (44.4)	6 (40.0)
Non-ocular adverse events	16 (66.7)	7 (77.8)	9 (60.0)
Death	0	0	0
Serious adverse events other than death	2 (8.3)	1 (11.1)	1 (6.7)
Adverse events leading to treatment discontinuation	0	0	0
Sight-threatening adverse events	0	0	0
Ocular adverse events assessed as causally related to study drug	0	0	0
Serious ocular adverse events assessed as causally related to study drug	0	0	0
Non-ocular adverse events assessed as causally related to study drug	0	0	0
Serious non-ocular adverse events assessed as causally related to study drug	0	0	0
All adverse events occurring in the study eye of subjects with PXE			
Conjunctival haemorrhage	2 (8.3)	1 (11.1)	1 (6.7)
Dry eye	2 (8.3)	1 (11.1)	1 (6.7)
Blepharospasm	1 (4.2)	1 (11.1)	—
Conjunctivitis allergic	1 (4.2)	1 (11.1)	—
All non-ocular adverse events observed in subjects with PXE			
Nasopharyngitis	4 (16.7)	2 (22.2)	2 (13.3)
COVID-19	3 (12.5)	1 (11.1)	2 (13.3)
Arthralgia	3 (12.5)	2 (22.2)	1 (6.7)
Hand dermatitis	2 (8.3)	2 (22.2)	—
Contusion	2 (8.3)	1 (11.1)	1 (6.7)
Tinea cruris	1 (4.2)	1 (11.1)	—
Upper respiratory tract infection	1 (4.2)	1 (11.1)	—
Ankle fracture	1 (4.2)	1 (11.1)	—
Dermal cyst	1 (4.2)	1 (11.1)	—
Hypoaesthesia	1 (4.2)	1 (11.1)	—
Nausea	1 (4.2)	1 (11.1)	—
Pyrexia	1 (4.2)	1 (11.1)	—
Acute cholecystitis	1 (4.2)	1 (11.1)	—
Cholelithiasis	1 (4.2)	1 (11.1)	—
Blood pressure increased	1 (4.2)	1 (11.1)	—
Hypertonic bladder	1 (4.2)	1 (11.1)	—
Ovarian cyst	1 (4.2)	1 (11.1)	—
Hypertension	1 (4.2)	1 (11.1)	—

Number of subjects with event (Incidence (%))

—: Event term is not listed, and "0" is not stated explicitly in the adverse event summary report.

a) Including 1 subject with possible PXE, 5 subjects in whom PXE was ruled out, and 9 subjects without results of PXE assessment.

Based on the above, faricimab should have acceptable safety in patients with CNV associated with AS, provided that the package insert includes similar warnings/precautions as with the currently approved indications.

PMDA's view:
Although the results should be interpreted with caution due to the limited number of patients enrolled in Study JR44390, there has been no specific new concerns about the safety of faricimab in patients with CNV associated with AS. Faricimab should have acceptable safety, in view of its efficacy [see Section 7.R.2]. However, as with the currently approved indications of nAMD, DME, and RVO, the package insert should include precautionary statements about, particularly, endophthalmitis, intraocular inflammation, retinal detachment, retinal tear, increase in intraocular pressure, and arterial thromboembolic events.

In patients with PXE, which is the predominant cause of AS, the results of Study JR44390 did not show a trend towards increased incidences of systemic adverse events related to VEGF inhibition, including arterial thromboembolic events, as compared with patients with nAMD, DME, and RVO, which are approved indications. However, information on the risk of arterial thromboembolic events should be provided appropriately to healthcare professionals in clinical practice, through the package insert etc.

7.R.4 Clinical positioning and indication

The applicant's explanation about the clinical positioning of and indication for faricimab:
For the treatment of CNV associated with AS, laser photocoagulation, PDT, transpupillary thermotherapy, and macular translocation therapy have been used, but have poor outcomes, e.g., a high recurrence rate of CNV, and it is often difficult to maintain visual acuity (*Today's Therapy in Ophthalmology*, the 3rd edition. Igaku-Shoin; 2017. p529-32). Although treatment with intravitreal VEGF inhibitors has been shown to improve or stabilize visual acuity and central retinal thickness (*Retina*. 2013; 33: 1300-14), no VEGF inhibitors have been approved for the indication of CNV associated with AS in Japan.

Faricimab is considered to contribute to both the stabilization of the pathological ocular vasculature and the inhibition of angiogenesis by inhibiting both the VEGF-A and Ang-2 pathways. Study JR44390 in patients with CNV associated with AS demonstrated the efficacy [see Section 7.R.2] and acceptable safety of faricimab [see Section 7.R.3].

Based on the above, since faricimab can become a new treatment option for CNV associated with AS, the proposed indication of "neovascular angioid streaks" is appropriate.

PMDA's view:
Study JR44390 demonstrated the efficacy of faricimab [see Section 7.R.2], and its safety should also be acceptable as long as similar safety measures as those for the currently approved indications are taken [see Section 7.R.3]. Thus, faricimab can be positioned as a new treatment option for CNV associated with AS. Given that Study JR44390 was conducted in patients with CNV associated with AS, the appropriate indication should be "choroidal neovascularization associated with angioid streaks."

7.R.5 Dosage and administration

The applicant's explanation about the rationale for the dosing regimen of faricimab in Study JR44390 and the appropriateness of the proposed dosage and administration based on the results of this study etc.:

In the development of faricimab for the currently approved indications, a higher dose of faricimab was associated with longer intraocular VEGF and Ang-2 suppression, and 6 mg of faricimab was the highest dose that was well tolerated in patients. Thus, only a dose level of faricimab 6 mg was selected for Study JR44390.

Given the following points, 3 consecutive Q4W doses during the initial dosing phase followed by pro re nata (PRN) dosing during the maintenance phase was selected for Study JR44390.

- For initial treatment of patients with CNV associated with AS, it is recommended that a VEGF inhibitor should be administered as 3 consecutive Q4W injections to improve or stabilize visual acuity (*Retina*. 2019; 39: 1-11).
- As to the dosing interval during the maintenance phase following the initial dosing phase in patients with CNV associated with AS, PRN dosing is generally used to minimize the risk of thromboembolic events such as ischemic heart disease and ischemic cerebral infarction in patients with PXE (the predominant cause of AS) and the risk of RPE atrophy caused by repeated administration of VEGF inhibitors (*Retina*. 2018; 38: 1464-77, *Middle East Afr J Ophthalmol*. 2017; 24: 136-42, etc.).

Then, based on the following results of Study JR44390, etc., the dose of faricimab for CNV associated with AS should be 6 mg, and the package insert should specify the minimum dosing interval (Q4W) only and then advise that disease activity should be assessed periodically, and that if a finding suggestive of disease activity is observed, additional dosing should be considered.

- As to the BCVA change from baseline, consistent improvement was observed from baseline through Week 12. The lower limit of the 90% CI was above the pre-specified threshold of 0 letters at the primary analysis time point of Week 12, and efficacy was sustained until Week 48 (Figure 1).
- Numerical improvement in the mean change from baseline in the BCVA score was observed even at Weeks 4 and 8 (Figure 1). The maximum BCVA was achieved at Week 4 in 7 subjects, at Week 8 in 7 subjects, and at Week 12 in 10 subjects. The number of injections of faricimab required to achieve the maximum BCVA differed from patient to patient. Based on the above, the number of initial consecutive doses should be determined based on each patient's response to treatment, instead of uniformly specifying the number of doses as 3.
- The number of injections of faricimab through Week 48 (median [min., max.]) was 6.5 [3, 13], and the number of injections to maintain the efficacy of faricimab differed from patient to patient. Thus, the dosing interval during the maintenance phase should not be specified uniformly, and it is desirable that the physician should determine the need for dosing based on each patient's disease condition, also to avoid overtreatment.

PMDA's view:
Since Study JR44390 demonstrated the efficacy of faricimab 6 mg in patients with CNV associated with AS [see Section 7.R.2], and its safety was also acceptable [see Section 7.R.3], there is no problem with the proposed 6 mg dose of faricimab for CNV associated with AS.

During the initial dosing phase, all patients received faricimab Q4W for 3 consecutive doses in Study JR44390, which demonstrated the efficacy of faricimab. However, given the applicant's explanation and the following points, allowing the physician to appropriately determine the number of initial consecutive doses for each patient, instead of uniformly specifying the number of initial consecutive doses in the DOSAGE AND ADMINISTRATION section, is justified.

- In patients with AS, repeated administration of VEGF inhibitors may pose a risk of RPE atrophy.
- In patients with PXE (the predominant cause of AS), no particular safety concerns were identified in Study JR44390, but repeated administration of VEGF inhibitors may pose a risk of thromboembolic events such as ischemic heart disease and ischemic cerebral infarction.
- Intravitreal injection imposes a heavy physical and psychological burden on patients.

In Study JR44390, after 3 consecutive Q4W doses as initial treatment, improved visual acuity was generally sustained with PRN administration [see Section 7.R.2], and no safety concerns were identified [see Section 7.R.3]. Thus, there is no problem with the applicant's measures (the package insert will advise that the physician should assess disease activity periodically after the first dose, and that if a finding suggestive of disease activity is observed, additional dosing should be considered.).

7.R.6 Post-marketing investigations

The applicant's explanation:
Based on the following observations, no concerns unique to patients with CNV associated with AS have been identified that would warrant further investigation in the post-marketing setting. Thus, rather than conducting additional pharmacovigilance activities including post-marketing surveillance in patients with CNV associated with AS, appropriate risk minimization measures should be considered and implemented promptly as needed based on the information obtained from routine pharmacovigilance activities, and the information should be provided to healthcare professionals in clinical practice.

- The safety profile of faricimab in Study JR44390 in patients with CNV associated with AS was similar to that observed for the currently approved indications, and there were no safety concerns unique to patients with CNV associated with AS [see Section 7.R.3].
- Patients with PXE have been reported to have an increased risk of ischemic heart disease, ischemic cerebral infarction, etc. (*Retina*. 2019; 39: 1-11, *Jpn J Dermatol.* 2017; 127: 2447-54), whereas no safety concerns about faricimab in patients with PXE were observed in Study JR44390 [see Section 7.R.3].
- Based on the latest Japanese and foreign post-marketing safety data (collected from [redacted], 20[redacted] through [redacted], 20[redacted]; the estimated cumulative number of patients exposed to faricimab, [redacted] patients), the

incidence of adverse events was analyzed. The results revealed no new findings that significantly impact the safety profile of faricimab.

PMDA's view:

Based on the data from Study JR44390, there were no clear differences in the safety profile of faricimab between patients with CNV associated with AS and patients in the currently approved indications, nor were there any safety concerns in patients with PXE. Given these findings, at present, there is little need to conduct additional pharmacovigilance activities including post-marketing surveillance in patients with CNV associated with AS.

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 inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that faricimab has efficacy in the treatment of CNV associated with AS, and that faricimab has acceptable safety in view of its benefits. Faricimab is clinically meaningful because it offers a new treatment option for patients with CNV associated with AS. PMDA considers that the clinical positioning, indication, dosage and administration, and post-marketing investigations need to be further discussed at the Expert Discussion.

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

Review Report (2)

April 11, 2025

Product Submitted for Approval

Brand Name	(1) Vabysmo Solution for Intravitreal Injection 120 mg/mL
	(2) Vabysmo Kit for Intravitreal Injection 120 mg/mL
Non-proprietary Name	Faricimab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	(1) September 6, 2024
	(2) March 17, 2025[16)]

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 considerations in Sections "7.R.1 Strategy for efficacy evaluation of faricimab" and "7.R.2 Efficacy" in the Review Report (1), the efficacy of faricimab in patients with CNV associated with AS was demonstrated.

At the Expert Discussion, 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), faricimab should have acceptable safety, if the following requirements are met: (i) As with the currently approved indications of nAMD, DME, and RVO, the package insert includes precautionary statements about, particularly,

16) Although a marketing application for faricimab under the categories of drugs with new indications, drugs with new dosages, and drugs in additional dosage forms was filed on September 6, 2024, Vabysmo Kit for Intravitreal Injection 120 mg/mL was approved in March 2025. Accordingly, the application for faricimab was resubmitted under the categories of drugs with new indications and drugs with new dosages.

endophthalmitis, intraocular inflammation, retinal detachment, retinal tear, increase in intraocular pressure, and arterial thromboembolic events; and (ii) although in Study JR44390, no trend towards increased incidences of systemic adverse events related to VEGF inhibition was observed in patients with PXE (the predominant cause of AS), as compared with patients in the currently approved indications, appropriate information continues to be provided to healthcare professionals through the package insert and related materials.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA and made the following comment.

- At present, the expert advisors support PMDA's conclusion that there are no safety concerns in patients with PXE and that there is little need to conduct additional pharmacovigilance activities including post-marketing surveillance in patients with CNV associated with AS. They also support the measures proposed by the applicant i.e., promptly considering and implementing appropriate risk minimization activities as needed based on the information obtained from routine pharmacovigilance activities, and providing the information to healthcare professionals in clinical practice. However, the number of subjects enrolled in Study JR44390 was limited. Given this and other reasons, it is necessary to continue to closely monitor, in particular, the risk of arterial thromboembolic events in patients with PXE even after marketing.

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), faricimab can be positioned as a new treatment option for patients with CNV associated with AS, and the appropriate indication should be "choroidal neovascularization associated with angioid streaks."

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA. PMDA instructed the applicant to amend the proposed indication to "choroidal neovascularization associated with angioid streaks," and the applicant responded accordingly.

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), there is no problem with the proposed dosage and administration.

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

1.5 Risk management plan (draft)

PMDA's conclusion:

Based on the considerations in Section "7.R.6 Post-marketing investigations" in the Review Report (1), at present, there is little need to conduct additional pharmacovigilance activities including post-marketing surveillance in patients with CNV associated with AS.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA. PMDA has concluded that the risk management plan (draft) for faricimab should include the safety specification presented in Table 8, and that the applicant should conduct additional risk minimization activities presented in Table 9.

Table 8. Safety and efficacy specifications in the risk management plan (draft)[a)]

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infectious endophthalmitis • Intraocular inflammation • Rhegmatogenous retinal detachment and retinal tear • Retinal pigment epithelial tear (nAMD) • Increase in intraocular pressure	• Arterial thromboembolic events	• None
Efficacy specification		
・None		

a) No additions made for the present application.

Table 9. 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
• None	• None	• Develop information materials (a proper use guide) to be distributed to healthcare professionals • Develop information materials (a patient notebook) to be distributed to patients

a) Only activities relevant to the present application are listed.

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

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

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

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

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following condition. As the product has been designated as an orphan drug for the indication claimed in the present application, the re-examination period is 10 years.

Indications

Age-related macular degeneration with subfoveal choroidal neovascularization

Diabetic macular edema

Macular edema following retinal vein occlusion

Choroidal neovascularization associated with angioid streaks

(Underline denotes additions.)

Dosage and Administration

[Age-related macular degeneration with subfoveal choroidal neovascularization]

Faricimab (Genetical Recombination) at a dose of 6.0 mg (0.05 mL) should be administered by intravitreal injection every 4 weeks, usually for 4 consecutive doses (the loading phase). The number of injections should be reduced, as appropriate, according to symptoms. In the subsequent maintenance phase, intravitreal injections should be given, usually every 16 weeks. The dosing interval should be adjusted according to symptoms, but the minimum interval is 8 weeks.

[Diabetic macular edema]

Faricimab (Genetical Recombination) at a dose of 6.0 mg (0.05 mL) should be administered by intravitreal injection every 4 weeks, usually for 4 consecutive doses. The number of injections should be reduced, as appropriate, according to symptoms. Then, the dosing interval should be extended incrementally, usually to 16 weeks. The dosing interval should be adjusted according to symptoms, but the minimum interval is 4 weeks.

[Macular edema following retinal vein occlusion, and Choroidal neovascularization associated with angioid streaks]

Faricimab (Genetical Recombination) at a dose of 6.0 mg (0.05 mL) should be administered by intravitreal injection. The minimum dosing interval is 4 weeks.

(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)
Ang-2	angiopoietin-2
AS	angioid streaks
BCVA	best corrected visual acuity
bevacizumab	Bevacizumab (Genetical Recombination)
brolucizumab	Brolucizumab (Genetical Recombination)
CI	confidence interval
CNV	choroidal neovascularization
CST	central subfield thickness
CTD	common technical document
DME	diabetic macular edema
ETDRS	early treatment diabetic retinopathy study
FA	fluorescein angiography
faricimab	Faricimab (Genetical Recombination)
ICH E9 guideline	"Statistical Principles for Clinical Trials" (PMSB/ELD Notification No. 1047 dated November 30, 1998)
MedDRA	medical dictionary for regulatory activities
MMRM	mixed-effect models for repeated measures
nAMD	neovascular age-related macular degeneration
OCT	optical coherence tomography
PDT	photodynamic therapy
PMDA	Pharmaceuticals and Medical Devices Agency
PRN	pro re nata
PT	preferred term
PXE	pseudoxanthoma elasticum
Q4W	every 4 weeks
ranibizumab	Ranibizumab (Genetical Recombination)
RMP	risk management plan
RPE	retinal pigment epithelium
RVO	retinal vein occlusion
SMQ	standard MedDRA Queries
Vabysmo	Vabysmo Solution for Intravitreal Injection 120 mg/mL
VEGF	vascular endothelial growth factor