Review Report

October 7, 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	Beovu Kit for Intravitreal Injection 120 mg/mL
Non-proprietary Name	Brolucizumab (Genetical Recombination) (JAN*)
Applicant	Novartis Pharma K.K.
Date of Application	December 12, 2024
Dosage Form/Strength	Aqueous solution for injection: Each syringe (0.165 mL) contains 19.8 mg of brolucizumab (genetical recombination).
Application Classification	Prescription drug, (4) Drug with a new indication and (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of proliferative diabetic retinopathy, and that the product has acceptable safety in view of its benefits (see Attachment). PMDA has also concluded that it is possible to add a dosing regimen of intravitreal injection every 6 weeks for 2 or 3 doses in the loading phase for the treatment of age-related macular degeneration with subfoveal choroidal neovascularization.

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.

Indications

○ Age-related macular degeneration with subfoveal choroidal neovascularization
○ Diabetic macular edema
○ <u>Proliferative diabetic retinopathy</u>

(Underline denotes additions.)

Dosage and Administration

Age-related macular degeneration with subfoveal choroidal neovascularization

The recommended dosage in the loading phase is 6 mg (0.05 mL) of brolucizumab (genetical recombination), administered by intravitreal injection once every 4 weeks for 3 consecutive doses ~~(loading phase)~~. Alternatively, the same dose may be administered by intravitreal injection once every 6 weeks for 2 consecutive doses. An additional dose may be administered based on the patient's condition. Subsequently, in the maintenance phase, the same dose is administered by intravitreal injection, usually once every 12 weeks. The dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 weeks.

Diabetic macular edema

The recommended dosage is 6 mg (0.05 mL) of brolucizumab (genetical recombination), administered by intravitreal injection once every 6 weeks, usually for 5 consecutive doses (loading phase). The number of doses may be reduced as appropriate based on the patient's condition. Subsequently, in the maintenance phase, the same dose is administered by intravitreal injection, usually once every 12 weeks. The dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 weeks.

Proliferative diabetic retinopathy

The recommended dosage is 6 mg (0.05 mL) of brolucizumab (genetical recombination), administered by intravitreal injection once every 6 weeks, usually for 3 consecutive doses (loading phase). The number of doses may be adjusted as appropriate based on the patient's condition. Subsequently, in the maintenance phase, the same dose is administered by intravitreal injection, usually once every 12 weeks. The dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 weeks.

(Underline denotes additions, and strikethrough denotes deletions.)

Approval Condition

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

* *Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

August 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	Beovu Kit for Intravitreal Injection 120 mg/mL
Non-proprietary Name	Brolucizumab (Genetical Recombination)
Applicant	Novartis Pharma K.K.
Date of Application	December 12, 2024
Dosage Form/Strength	Aqueous solution for injection: Each syringe (0.165 mL) contains 19.8 mg of brolucizumab (genetical recombination).

Proposed Indications

○ Age-related macular degeneration with subfoveal choroidal neovascularization
○ Diabetic macular edema
○ Proliferative diabetic retinopathy

(Underline denotes additions.)

Proposed Dosage and Administration

Age-related macular degeneration with subfoveal choroidal neovascularization

The recommended dosage is 6 mg (0.05 mL) of brolucizumab (genetical recombination), administered by intravitreal injection once every 4 weeks for 3 consecutive doses (loading phase). Alternatively, the same dose may be administered by intravitreal injection once every 6 weeks for 2 consecutive doses (loading phase), or for 3 consecutive doses (loading phase) based on the patient's condition. Subsequently, in the maintenance phase, the same dose is administered by intravitreal injection, usually once every 12 weeks. The dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 weeks.

Diabetic macular edema

The recommended dosage is 6 mg (0.05 mL) of brolucizumab (genetical recombination), administered by intravitreal injection once every 6 weeks, usually for 5 consecutive doses (loading phase). The number of doses may be reduced as appropriate based on the patient's condition. Subsequently, in the maintenance phase, the same dose is administered by intravitreal injection, usually once every 12 weeks. The dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 weeks.

Proliferative diabetic retinopathy

The recommended dosage is 6 mg (0.05 mL) of brolucizumab (genetical recombination), administered by intravitreal injection once every 6 weeks, usually for 3 consecutive doses (loading phase). The number of doses may be adjusted as appropriate based on the patient's condition. Subsequently, in the maintenance phase, the

same dose is administered by intravitreal injection, usually once every 12 weeks. The dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 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

Brolucizumab (genetical recombination) (hereinafter referred to as "brolucizumab") is a recombinant single-chain antibody that consists of the variable regions of the heavy and light chains of a humanized anti-human vascular endothelial growth factor (VEGF)-A monoclonal antibody that are connected by a linker. In Japan, Beovu, the intravitreal injectable formulation of brolucizumab, was approved for the indications of "age-related macular degeneration with subfoveal choroidal neovascularization" in March 2020 and "diabetic macular edema" in June 2022.

Diabetic retinopathy (DR), a complication of diabetes mellitus, is caused by microvascular damage in the retina and is broadly classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) according to the presence or absence of retinal neovascularization. In PDR, the most advanced stage of DR, retinal neovascularization develops. These newly formed vessels are fragile and prone to bleeding, resulting in complications such as vitreous hemorrhage, preretinal hemorrhage, and retinal detachment, which can lead to severe visual impairment (Diabetic Retinopathy Clinical Practice Guidelines [First Edition]. *Journal of Japanese Ophthalmological Society*. 2020;124:955-981 [hereinafter referred to as "Japanese diabetic retinopathy clinical practice guideline], *Saudi J Ophthalmol*. 2018;32:318-323). It has been reported that retinal neovascularization in PDR is caused by increased VEGF production under ischemic conditions as a result of the occlusion of retinal capillaries (*Nat Rev Dis Primers*. 2016;2:16012). In view of these findings, brolucizumab is expected to have a therapeutic effect on PDR. In Japan, clinical studies to develop brolucizumab for PDR began in November 2020. The applicant has submitted a partial change application, considering that the efficacy and safety of brolucizumab for PDR were demonstrated based on the results of Japanese and foreign clinical studies. Outside Japan, applications for the indication of PDR are under review in China and [redacted] as of July 2025.

Brolucizumab has been approved for neovascular age-related macular degeneration (nAMD) with the following dosage and administration: intravitreal injection of 6 mg once every 4 weeks (Q4W) for 3 consecutive doses in the loading phase, followed by intravitreal injection of 6 mg in the maintenance phase, usually once every 12 weeks (Q12W) (the dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 weeks). The present application also included a partial change application based on the results of population pharmacokinetic (PPK)/pharmacodynamic (PD) analysis, to add a new dosing regimen of intravitreal injection once every 6 weeks (Q6W) for 2 or 3 consecutive doses in the loading phase for nAMD. Outside Japan, this dosing regimen of brolucizumab 6 mg Q6W for 2 or 3 consecutive doses in the loading phase for nAMD was approved in Europe in June 2023 based on the results of PPK/PD analysis.

2. Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for an additional indication and an additional dosing regimen, no data relating to quality have been submitted.

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

The present application is intended for an additional indication and an additional dosing regimen. No additional study results have been submitted because the non-clinical pharmacology data have already been evaluated for the initial approval of brolucizumab.

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

The present application is intended for an additional indication and an additional dosing regimen. No additional study results have been submitted because the non-clinical pharmacokinetic data have already been evaluated for the initial approval of brolucizumab.

5. Toxicology and Outline of the Review Conducted by PMDA

Since the present application is intended for an additional indication and an additional dosing regimen, no toxicity data have been submitted.

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

6.1 Biopharmaceutic studies and associated analytical methods

No data on biopharmaceutic studies and associated analytical methods have been submitted.

6.2 Clinical pharmacology

The applicant submitted the results of PPK and PPK/PD analyses using data obtained from clinical studies in nAMD patients as the main data on clinical pharmacology studies. The present application also includes the addition of an indication for PDR. No clinical pharmacology study results in PDR patients have been submitted, because brolucizumab is locally administered by intravitreal injection and no particular differences in its pharmacokinetics have been observed between the approved indications (nAMD and diabetic macular edema [DME]).

6.2.1 Population analysis

6.2.1.1 PPK analysis (Reference, CTD 5.3.3.5-1)

PPK analysis (NONMEM version 7.4.3) was performed using the pharmacokinetic data of brolucizumab in serum (183 subjects, 947 collection time points) obtained from a foreign phase I study (Study C-10-083) and a global phase II study (Study RTH258-E003 [hereinafter referred to as "Study E003"]) conducted in nAMD patients. The pharmacokinetics of brolucizumab was described using a 1-compartment model with first-order absorption. Age, sex, and race were evaluated as covariates for systemic clearance and the elimination rate constant from the vitreous body. However, none were included in the final model. In the final model, the elimination half-life of brolucizumab in the vitreous body was estimated to be 4.4 days.

6.2.1.2 PPK/PD analysis (Reference, CTD 5.3.4.2-2 and CTD 5.3.4.2-3)

PPK/PD analysis (NONMEM version 7.4.3) was performed using data of central subfield thickness (CSFT) and best-corrected visual acuity (BCVA) (2100 subjects) obtained from a foreign phase I study (Study C-10-

083), a foreign phase II study (Study C-12-006), a global phase III study (Study RTH258-C001 [hereinafter referred to as "Study C001"]), and a foreign phase III study (Study RTH258-C002 [hereinafter referred to as "Study C002"]) conducted in nAMD patients.

For the pharmacokinetics of brolucizumab in the eye following intravitreal injection, a 1-compartment model was assumed. The elimination half-life in the vitreous body was fixed at 4.4 days [see Section 6.2.1.1] and the vitreous volume was fixed at 4.0 mL (*Handbook of Biomaterial Properties Second Edition*. Springer; 2016. p127). The relationship between the intravitreal brolucizumab concentration estimated based on the assumed model and the time course of CSFT[1)] was described using an indirect response model combined with a logistic model. For analysis of the relationship between a decrease in CSFT and the change in BCVA, an effect compartment was incorporated into the model to account for the delayed change in BCVA following the decrease in CSFT caused by administration of brolucizumab. The logit-transformed change in BCVA was described using a power model. The final model of CSFT and BCVA incorporated the following covariates: baseline CSFT for CSFT change due to disease progression or treatment; baseline BCVA and age for the maximum improvement effect in BCVA[2)]; and baseline BCVA for the additive residual error in BCVA.

The change from baseline in BCVA was simulated based on this PPK/PD model using the patient populations of Studies C001 and C002 following intravitreal injection of brolucizumab 6 mg Q4W for 3 consecutive doses or Q6W for 2 consecutive doses (3 consecutive doses when disease activity was present[3)]) in the loading phase, followed by maintenance dosing of brolucizumab 6 mg Q12W (Q8W when disease activity was present[4)]). The results showed that the time course of the change from baseline in BCVA was predicted to be similar regardless of the assumed dosing regimens in the loading phase (Figure 1).

1) CSFT was modeled as the sum of the retinal thickness that does not change with disease progression or treatment (normal retinal thickness) and the retinal thickness that changes with disease progression or treatment (disease-induced retinal thickness).
2) Coefficient (intercept after log transformation) of the power model for BCVA change.
3) If disease activity was present, defined as CSFT >340 μm at Week 12, brolucizumab 6 mg was to be administered at Week 12 and thereafter at Q8W intervals.
4) CSFT was estimated every 12 weeks. If disease activity was present, defined as CSFT >340 μm or a change in CSFT of >75 μm from Week 12, brolucizumab was to be administered thereafter at Q8W intervals.

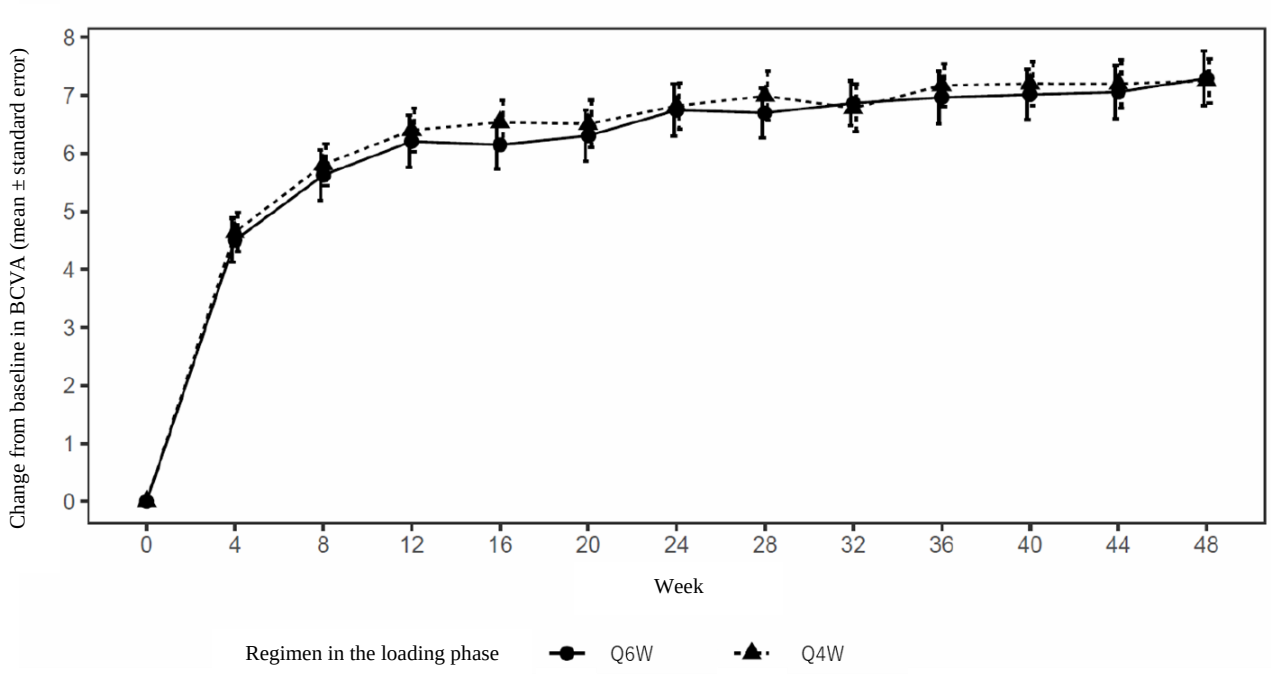

Figure 1. Predicted values of the change from baseline in BCVA score up to Week 48 by loading phase dosing regimen in the patient populations of Studies C001 and C002 (mean ± standard error)

Using the constructed PPK/PD model, the time course of the change from baseline in BCVA in the patient populations of Studies C001 and C002 following intravitreal injection of brolucizumab at the dosing regimens used in each study[5)] was calculated by empirical Bayes estimation. The calculated time course of the change from baseline in BCVA was generally consistent with those (observed values) in the brolucizumab groups of Studies C001 and C002 (Table 1).

Table 1. Change from baseline in BCVA during Q4W loading phase dosing (observed and estimated values)

	Study C001				Study C002	
	Brolucizumab 3 mg		Brolucizumab 6 mg		Brolucizumab 6 mg	
Evaluation time point	Observed value	Estimated value	Observed value	Estimated value	Observed value	Estimated value
Week 4	3.7 ± 0.44 3.0 (−36.0, 37.0)	4.7 ± 0.42 3.5 (−23.9, 41.7)	3.7 ± 0.51 3.0 (−57.0, 46.0)	4.6 ± 0.46 3.5 (−26.5, 38.2)	3.7 ± 0.37 3.0 (−28.0, 36.0)	4.9 ± 0.42 3.7 (−24.5, 38.5)
Week 8	5.7 ± 0.47 5.0 (−30.0, 53.0)	5.8 ± 0.48 4.8 (−23.9, 41.7)	5.5 ± 0.56 5.0 (−62.0, 42.0)	5.9 ± 0.50 4.8 (−26.6, 43.5)	5.1 ± 0.43 5.0 (−33.0, 41.0)	6.0 ± 0.45 5.0 (−27.2, 41.7)
Week 12	5.9 ± 0.52 5.0 (−32.0, 53.0)	6.4 ± 0.59 5.6 (−26.7, 45.7)	6.3 ± 0.59 7.0 (−38.0, 44.0)	6.4 ± 0.58 5.4 (−28.1, 43.2)	5.7 ± 0.44 5.0 (−32.0, 39.0)	6.7 ± 0.41 5.8 (−27.4, 43.2)
Week 16	5.8 ± 0.59 6.0 (−55.0, 55.0)	6.4 ± 0.61 5.3 (−25.6, 43.6)	6.7 ± 0.57 6.0 (−44.0, 41.0)	6.5 ± 0.60 5.5 (−29.2, 46.2)	5.7 ± 0.46 6.0 (−32.0, 35.0)	6.8 ± 0.46 6.0 (−28.6, 44.8)
Week 20	6.7 ± 0.57 6.0 (−51.0, 55.0)	6.5 ±0.55 5.5 (−27.2, 44.3)	6.7 ± 0.62 7.0 (−38.0, 44.0)	6.5 ± 0.60 5.5 (−28.2, 46.3)	5.8 ± 0.51 6.0 (−29.0, 38.0)	6.8 ± 0.53 6.0 (−27.8, 43.1)
Week 48	7.0 ± 0.66 8.0 (−47.0, 51.0)	7.2 ± 0.60 6.4 (−26.2, 47.7)	7.5 ± 0.77 8.0 (−50.0, 52.0)	7.2 ± 0.56 6.6 (−28.9, 46.4)	7.8 ± 0.54 8.0 (−21.0, 40.0)	7.6 ± 0.50 7.0 (−29.5, 45.0)

Upper row: mean ± standard error; lower row: median (minimum, maximum).

[5)] Brolucizumab 3 or 6 mg was to be intravitreally injected at Q4W for a total of 3 doses as loading treatment, followed by intravitreal injection of brolucizumab 3 or 6 mg Q12W as maintenance treatment. CSFT was estimated every 12 weeks. If disease activity was present, defined as CSFT >340 μm or a change in CSFT of >75 μm from Week 12, brolucizumab was to be administered thereafter at Q8W intervals.

6.R Outline of the review conducted by PMDA

6.R.1 Dosage and administration for nAMD

The applicant's explanation:

It is possible to add a dosing regimen of brolucizumab 6 mg Q6W for 2 or 3 consecutive intravitreal injections as a dosing regimen of brolucizumab in the loading phase for nAMD based on the following considerations:

The approved dosing regimen in the loading phase for nAMD is brolucizumab 6 mg administered by intravitreal injection Q4W for 3 consecutive doses. Intravitreal injection imposes a substantial burden on patients, and the need for frequent visits also imposes a substantial burden both on patients and the medical institutions. For these reasons, a PPK/PD model was used to investigate a dosing interval and numbers of doses that are expected to achieve efficacy comparable to that of the approved regimen, while reducing the burden.

Based on the results of the simulation using the constructed PPK/PD model [see Section 6.2.1.2], administration of brolucizumab 6 mg Q6W for 2 consecutive doses (3 consecutive doses when disease activity is present) in the loading phase is expected to achieve efficacy comparable to that of the approved dosing regimen of brolucizumab 6 mg Q4W for 3 consecutive doses (Figure 1). In addition, the dosing regimen of brolucizumab 6 mg Q6W for 2 or 3 consecutive doses allows a longer dosing interval and the same or a smaller number of doses in the loading phase than the approved dosing regimen , and is therefore unlikely to raise new safety concerns.

In view of the above, it is meaningful to add the treatment option of brolucizumab Q6W for 2 or 3 consecutive doses as a dosing regimen of brolucizumab in the loading phase.

PMDA's view:

In view of the above applicant's explanation and the physical and psychological burden of intravitreal injection on patients and others, it is meaningful to evaluate an option of extending the dosing interval of brolucizumab and reducing the number of doses in the loading phase. Taken together with the simulation results of the change from baseline in BCVA based on the PPK/PD model (Figure 1), the dosing regimen of intravitreal injection of brolucizumab 6 mg Q6W for 2 consecutive doses, or 3 consecutive doses when disease activity is present, in the loading phase is unlikely to be inferior to the approved dosing regimen in terms of efficacy and is also unlikely to raise new safety concerns. It is therefore possible to add the intravitreal injection of brolucizumab 6 mg Q6W for 2 consecutive doses, or 3 consecutive doses when disease activity is present, as a dosing regimen of brolucizumab in the loading phase for nAMD.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from the clinical study shown in Table 2.

Table 2. List of clinical studies on efficacy and safety

Data category	Region	Study identifier CTD	Phase	Population	Number of subjects randomized	Outline of dosing regimen	Main endpoints
Evaluation	Global	Study D2301 5.3.5.1-1	III	PDR patients	689	Brolucizumab group: Brolucizumab 6 mg was intravitreally injected Q6W for a total of 3 doses. → Brolucizumab 6 mg was intravitreally injected Q12W up to Week 48 and Q12W to Q24W from Weeks 48 to 90 (additional injections were allowed). PRP group: The initial treatment was given by Week 12, and PRP was thereafter performed according to disease activity.	Efficacy Safety

7.1 Global phase III study (CTD 5.3.5.1-1: Study CRTH258D2301 [Study D2301]; November 2020 to August 2024)

A randomized, single-masked, parallel-group, comparative study using panretinal photocoagulation (PRP) as the control was conducted in 15 countries or regions including Japan[6)] to investigate the efficacy and safety of brolucizumab in PDR patients[7)] (target sample size; 353 subjects per group for a total of 706 subjects[8)]). The primary analysis was performed at the time point when all subjects had completed the assessment at Week 54 or discontinuation, and the final analysis was performed at the time point when all subjects had completed the assessment at Week 96 or discontinuation.

The dosing regimen was as follows: Subjects were randomized in a 1:1 ratio to the brolucizumab group or PRP group.[9)] In the brolucizumab group, brolucizumab 6 mg Q6W was intravitreally injected into the study eye for a total of 3 doses, followed by Q12W dosing up to Week 48 under single-masked conditions.[10)] From Week 48 onward, the dosing interval was adjusted among Q12W, Q18W, or Q24W based on the assessment of disease activity.[11)] However, at the scheduled study visits every 6 weeks after Week 18, additional injections of brolucizumab 6 mg were allowed as needed based on the assessment of disease activity. In the PRP group, the initial treatment was started on Day 1, and laser irradiation was performed in 2 to 4 sessions. The initial treatment had to be completed by Week 12. From Week 18 onward, additional PRP was performed as needed based on the assessment of disease activity.

All of the 689 randomized subjects (347 in the brolucizumab group and 342 in the PRP group; the same order applies hereinafter) received the study treatment and were included in the safety analysis set and the full

6) Argentina, Australia, Brazil, Canada, Chile, China, India, Japan, South Korea, Mexico, the Philippines, Russia, Taiwan, Türkiye, and the US.

7) Patients with type 1 or 2 diabetes mellitus aged ≥18 years with a hemoglobin A1c (HbA1c) level of ≤12% at screening whose study eye met the following criteria:
- PDR confirmed by the investigator using color fundus photography and fundus fluorescein angiography.
- BCVA with an early treatment diabetic retinopathy study (ETDRS) letter score of ≥34 at screening and at baseline.
- No previous treatment with PRP.

8) The target sample size (353 subjects per group) was determined to provide >99% power for the primary endpoint, namely, the change from baseline in BCVA at Week 54, assuming a between-group difference of 0 letters, a standard deviation of 10 letters, a dropout rate of 15%, a non-inferiority margin of −4 letters, and a one-sided significance level of 2.5%. In the determination of the sample size, assessment of secondary endpoints, etc. was also taken into account.

9) Stratified allocation was performed using region (US and Canada, East Asia, and other regions) as a stratification factor.

10) Assessors of BCVA and peripheral vision were masked to the assignment of study treatment. The central assessor of color fundus images was masked to the assignment of study treatment, the study visit time point, and the investigator's assessment of disease activity.

11) The presence or absence of disease activity was determined by the investigator based on retinal imaging and visual function assessment.

analysis set (FAS). The FAS was used as the primary efficacy analysis population.[12)] A total of 59 subjects (30 and 29 subjects) discontinued the study by Week 54, the primary efficacy analysis time point, and the main reasons for discontinuation were withdrawal of consent (13 and 12 subjects), lost to follow-up (7 and 8 subjects), death (6 and 3 subjects), and adverse events (2 and 4 subjects). A total of 101 subjects (46 and 55 subjects) discontinued the study by Week 96, and the main reasons for discontinuation were withdrawal of consent (20 and 20 subjects), lost to follow-up (11 and 13 subjects), death (8 and 9 subjects), investigator's decision (4 and 6 subjects), and adverse events (3 and 5 subjects).

Table 3 shows the change from baseline in BCVA at Week 54, which was assessed as the primary endpoint. The between-group difference [95% confidence interval (CI)] for the least squares mean of the change was 4.4 [2.4, 6.4] letters and the lower bound of the 95% CI was above the non-inferiority margin of −4 letters. Thus, the non-inferiority of brolucizumab to PRP was demonstrated. Figure 2 shows the change from baseline in BCVA up to Week 96.

Table 3. Change from baseline in BCVA at Week 54 (letters) (Study D2301, FAS, LOCF)

	Brolucizumab:	PRP:
BCVA at baseline[a)]	77.2 ± 10.2 (347)	77.0 ± 10.9 (342)
BCVA at Week 54[a)]	79.3 ± 11.7 (277)	76.3 ± 12.2 (246)
Change from baseline in BCVA at Week 54[b) c)]	0.2 ± 0.72 (342)	−4.2 ± 0.73 (337)
Between-group difference [95% CI][c)]	4.4 [2.4, 6.4]	-

-: Not applicable.

a) Mean ± standard deviation (number of subjects evaluated)

b) Least squares mean ± standard error (number of subjects evaluated)

c) Analysis of covariance with the following covariates: treatment group, centrally-assessed DR severity grade at baseline based on DRSS (NPDR, mild or moderate PDR, high-risk or worse PDR, ungradable), age (<55 years, ≥55 years), region (US and Canada, East Asia, or other regions), and BCVA at baseline. Missing values were imputed using the last observed value by the LOCF method. In the analysis, 5 subjects in the brolucizumab group and 5 subjects in the PRP group with missing data of the DR severity grade at baseline, one of the covariates in the analytical model, were excluded from the FAS. Data obtained after discontinuation of the study treatment were also included in the analysis. However, subjects who received alternative treatment other than the study treatment for DR or treatment relevant to DME (VEGF inhibitors and PRP other than the study treatment, periocular or intraocular corticosteroid therapy, grid and focal laser photocoagulation, or vitreous surgery) in the study eye were censored. Missing data after censoring were imputed using the last observation prior to receiving the relevant treatment. By Week 54, 13 (3.7%) subjects in the brolucizumab group and 51 (14.9%) subjects in the PRP group received alternative treatment other than the study treatment for DR or treatment relevant to DME in the study eye.

[12)] Although the FAS was defined as the primary efficacy analysis population, 10 subjects (5 in the brolucizumab group and 5 in the PRP group) had missing data of the DR severity grade at baseline, one of the covariates in the primary analysis model. Therefore, the primary analysis of the primary endpoint and various analyses using a similar analytical model excluded these 10 subjects and were performed in 679 subjects (342 in the brolucizumab group and 337 in the PRP group).

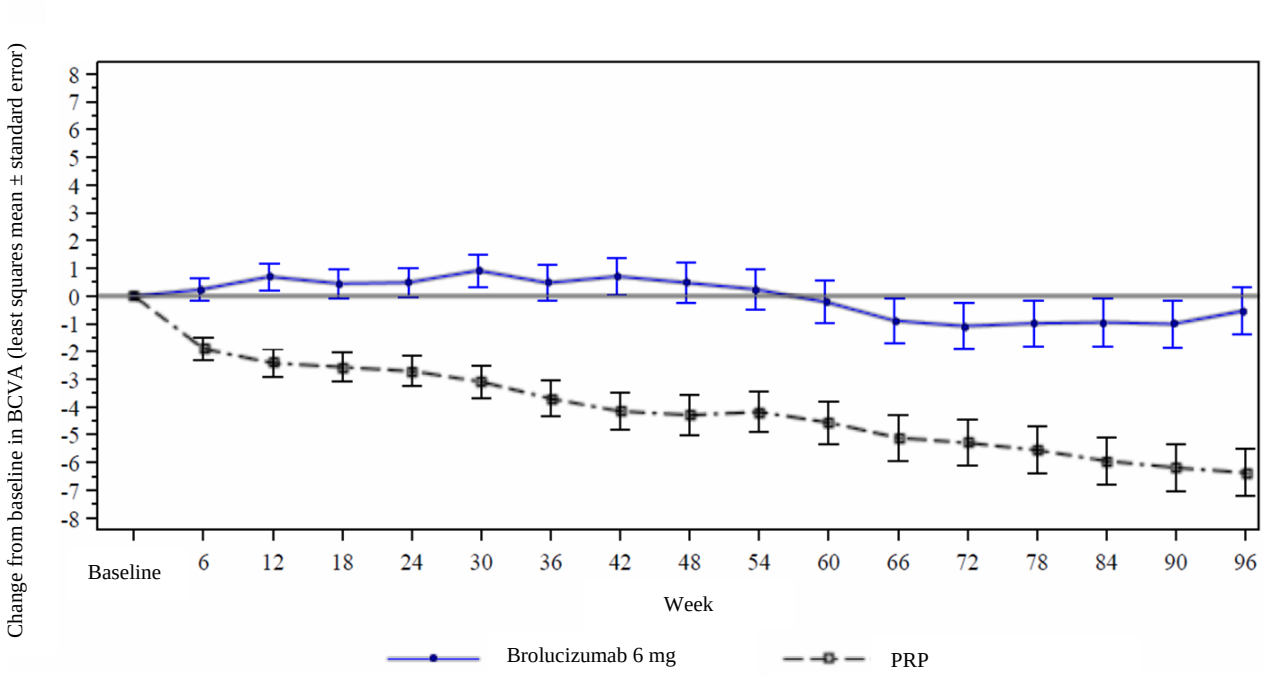

Figure 2. Time course of the change from baseline in BCVA up to Week 96 (Study D2301, least squares mean ± standard error, FAS, LOCF)

By Week 96, adverse events in the study eye were observed in 43.8% (152 of 347) of subjects in the brolucizumab group and 58.2% (199 of 342) of subjects in the PRP group, while non-ocular adverse events were observed in 65.1% (226 of 347) of subjects in the brolucizumab group and 63.5% (217 of 342) of subjects in the PRP group. Death was reported in 8 subjects in the brolucizumab group (cardiac arrest and COVID-19 in 2 subjects each, and acute cardiac event, cardiac failure acute, pneumonia, and gastric cancer in 1 subject each) and 9 subjects in the PRP group (acute myocardial infarction in 2 subjects, and cardiomegaly, coronary artery disease, ventricular arrhythmia, death, brain neoplasm, stroke, and intracranial aneurysm in 1 subject each). All of these deaths were assessed as unrelated to the study treatment. Table 4 shows the incidences of serious adverse events other than death.

Table 4. Incidences of serious adverse events other than death (Study D2301, safety analysis set)

Treatment group	Incidence		Breakdown
Brolucizumab	Study eye	3.7% (13/347)	Vitreous haemorrhage (2) in 3 subjects, uveitis (2) and retinal occlusive vasculitis (2) in 2 subjects each, and uveitis/retinal vasculitis (1), retinal artery occlusion, endophthalmitis (1), retinal detachment, intraocular pressure increased, and cataract in 1 subject each
	Non-ocular	17.9% (62/347)	Cerebral infarction (3) in 5 subjects, pneumonia in 3 subjects, hypertension and COVID-19 in 2 subjects each, and hyperglycaemia, cardiac failure congestive, cardiac failure acute, hyperglycaemia/mastitis, ischaemic stroke/renal failure, hypertension/measles/gastritis/peripheral vascular disorder, blood triglycerides increased, cardiac arrest, cellulitis, cerebral ischaemia, nausea/vomiting, ovarian adenoma, injury, gastric polyps, back pain, endocrine pancreatic disorder, gastric cancer stage III, gastric cancer, tenosynovitis stenosans, diabetic ketoacidosis, gastric perforation/renal failure, colorectal cancer, hypoglycaemia/stroke, generalised oedema, diabetes mellitus/hypertension, chronic kidney disease, gastric stenosis/gastric ulcer/gastric cancer, anaemia/angina unstable/urinary tract infection/end stage renal disease, cardiac failure acute/pneumonia/hypertension, acute respiratory failure/chest pain/constipation/nephropathy toxic/acute pulmonary oedema/head injury/hyperkalaemia/hypervolaemia/humerus fracture/loss of consciousness/hernia pain/periprocedural myocardial infarction/proteinuria/urinary tract infection/coronary artery disease, blood pressure abnormal, blood glucose increased/inguinal hernia, cholelithiasis/nephrolithiasis/meningioma, lung adenocarcinoma stage IV/escherichia infection/pleural effusion, osteomyelitis/localised infection, osteomyelitis, coronary artery disease, cardiac failure/coronary artery disease, atrial fibrillation/stroke/haemorrhagic stroke, neuropathic arthropathy, blood potassium increased/renal failure, pericarditis, oesophageal carcinoma, nephrolithiasis, ischaemic stroke/myocardial infarction/syncope, atrial flutter/bacteraemia/cellulitis/cardiogenic shock/gangrene/hypoxia/metabolic encephalopathy/acute cardiac event/oedema, cardiac arrest/pickwickian syndrome/systemic inflammatory response syndrome, hypoglycaemia, spinal cord injury, and uterine haemorrhage in 1 subject each
PRP	Study eye	8.8% (30/342)	Vitreous haemorrhage in 19 subjects, cataract in 3 subjects, tractional retinal detachment (1), diabetic retinopathy, and macular oedema (1) in 2 subjects each, and retinal haemorrhage and cataract cortical in 1 subject each
	Non-ocular	18.7% (64/342)	End stage renal disease and diabetic foot in 3 subjects each, and cerebellar infarction, acute myocardial infarction/diabetic ketoacidosis, stroke/ischaemic stroke/pneumonia, coronary artery disease, postoperative wound infection/ulna fracture/nephrolithiasis, inguinal hernia/sinus node dysfunction, myocardial infarction/coronary artery disease/pulmonary oedema, wound infection, ovarian cyst torsion/pelvic adhesions/endometriosis, arteriosclerosis coronary artery, ventricular arrhythmia, pneumonia bacterial, intervertebral disc protrusion, vertigo positional/otitis media chronic, cerebral infarction, diabetic nephropathy, humerus fracture/diabetes mellitus inadequate control/diabetic neuropathy, humerus fracture, chronic kidney disease, acute myocardial infarction/pneumonia bacterial, ascites/pyrexia, colorectal cancer, diabetes mellitus inadequate control, hypertension, cardiomegaly, erysipelas/diabetic neuropathy, myocardial infarction, cholelithiasis, uterine prolapse, palpitations, intervertebral disc degeneration/spinal osteoarthritis/spondylolisthesis, myalgia/hypertensive crisis, blood glucose increased, transient ischaemic attack, chest pain, headache, sepsis, cardiac failure congestive, cellulitis staphylococcal, cholecystitis, gangrene, abscess limb/cellulitis/diabetic foot/renal failure, generalised oedema/chronic kidney disease, pancreatitis/procedural haemorrhage, arthritis bacterial, pitted keratolysis/vomiting, osteomyelitis, coronary artery occlusion/thoracic vertebral fracture, skin ulcer, acute myocardial infarction, brain neoplasm, stroke, anaemia/endometrial cancer metastatic, benign ovarian tumour/intracranial aneurysm, dystonia, coma/breast cancer female, myocarditis, and ankle fracture in 1 subject each

The "Incidence" column shows the percentage of subjects with events (number of subjects with events/number of subjects evaluated). The "Breakdown" column shows the number of subjects with events; numbers in parentheses indicate the number of subjects with events assessed as related to the study treatment.

The incidences of adverse events assessed as related to the study treatment were as follows: Adverse events in the study eye were observed in 8.1% (28 of 347) of subjects in the brolucizumab group and 9.6% (33 of 342) of subjects in the PRP group. The events observed in ≥2 subjects in either group were vitreous haemorrhage (7 subjects in the brolucizumab group and 8 subjects in the PRP group; the same order applies hereinafter), uveitis (6 and 0 subjects), iridocyclitis (4 and 0 subjects), visual acuity reduced (3 and 0 subjects), eye inflammation (2 and 0 subjects), retinal occlusive vasculitis (2 and 0 subjects), retinal vasculitis (2 and 0 subjects), macular oedema (1 and 11 subjects), conjunctival haemorrhage (0 and 2 subjects), diabetic retinal oedema (0 and 4 subjects), and eye pain (0 and 6 subjects). Non-ocular adverse events were observed in 0.9% (3 of 347) of

subjects in the brolucizumab group and 0.6% (2 of 342) of subjects in the PRP group, and an event observed in ≥2 subjects in either group was cerebral infarction (3 and 0 subjects).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation about the plan of the global phase III study in PDR patients (Study D2301):

Study D2301 was planned as a global study including Japan, because the therapeutic effect of brolucizumab on PDR was considered unlikely to be affected by intrinsic or extrinsic ethnic factors in view of the following points:

- There are no major differences in the disease concept of PDR or its diagnostic criteria between Japan and foreign countries (Japanese diabetic retinopathy clinical practice guideline; Diabetic Retinopathy Preferred Practice Pattern. American Academy of Ophthalmology; 2024).
- At the planning stage of Study D2301, although ranibizumab (genetical recombination) (hereinafter referred to as "ranibizumab") or aflibercept (genetical recombination) (hereinafter referred to as "aflibercept") had been approved for the treatment of PDR or DR in some participating countries or regions, the standard treatment for PDR at that time was PRP in all participating countries or regions (*Ophthalmol Sci*. 2021;1:100037, *Cochrane Database Syst Rev*. 2018;3:sCD012314).
- Brolucizumab is an antibody fragment that is intravitreally injected with the expectation of a local effect in the eye, and no ethnic differences in efficacy, safety, or pharmacokinetics have been found in the clinical study results of brolucizumab in nAMD patients and DME patients.

Study D2301 was planned to demonstrate the non-inferiority of brolucizumab to PRP, which was the standard treatment for PDR in Japan and foreign countries at the time.

Since PDR is a disease with a high risk of reduced visual acuity, it is important to evaluate the visual outcomes. Therefore, the primary endpoint of Study D2301 was defined as the change from baseline in BCVA and the primary evaluation time point was set at Week 54, with reference to clinical studies that compared VEGF inhibitors and PRP in PDR patients (*JAMA Ophthalmol*. 2018;136:1138-1148, *Lancet*. 2017;389:2193-2203) and other information.

In the assessment of non-inferiority, visual acuity was evaluated using the ETDRS chart, which consists of 14 rows, each comprising 5 letters of equal size. In the clinical setting, an increase or decrease of ≥5 readable letters is considered a clinically significant change in visual acuity, irrespective of the underlying disease, whereas a change of ≤4 readable letters, which does not correspond to a change of 1 row on the chart, is considered clinically insignificant. Therefore, the non-inferiority margin was set at −4 letters, with reference to clinical studies of brolucizumab in other retinal diseases (Review Reports of "Beovu kit for intravitreal injection 120 mg/mL," dated January 14, 2020 and May 12, 2022) and other information.

The applicant's explanation about the efficacy of brolucizumab in PDR patients based on the results of Study D2301:

The non-inferiority of brolucizumab to PRP in terms of the change from baseline in BCVA at Week 54, the primary endpoint of Study D2301, was demonstrated [see Section 7.1]. Table 5 shows the results of the main secondary endpoints. The results of all secondary endpoints supported the results of the primary endpoint for brolucizumab.

Table 5. Results of the main secondary endpoints (Study D2301, FAS)

	Brolucizumab	PRP	Between-group difference [95% CI][a)]
Proportion of subjects in whom PDR was not observed at Week 54[b) c) d) e)]	63.6 (187/294)	22.4 (65/290)	39.4 [32.0, 46.8]
Proportion of subjects in whom DME involving the central fovea was observed by Week 54[c) f) g)]	31.1 (108/347)	72.7 (248/341)	−41.1 [−48.0, −34.2]
Proportion of subjects with a ≥2- step improvement from baseline in DRSS at Week 54[c) d) h)]	45.4 (128/282)	20.4 (57/279)	26.4 [19.5, 33.3]
Proportion of subjects with a ≥3- step improvement from baseline in DRSS at Week 54[c) d) h)]	20.6 (58/282)	10.8 (30/279)	10.2 [5.2, 15.2]

% (number of applicable subjects/number of subjects evaluated)

a) Brolucizumab group - PRP group

b) Subjects with DRSS score ≥61 were classified as PDR.

c) The between-group difference was calculated by the Mantel-Haenszel method with the following stratification factors: centrally-assessed DR severity grade at baseline based on DRSS (NPDR, mild or moderate PDR, high-risk or worse PDR, ungradable), age (<55 years, ≥55 years), and region (US and Canada, East Asia, or other regions). The 95% CI for the between-group difference was calculated based on the normal approximation to the binomial distribution. Missing values were imputed using the last observed value by the LOCF method.

d) Subjects who received alternative treatment other than the study treatment for DR or treatment relevant to DME (VEGF inhibitors and PRP other than the study treatment, periocular or intraocular corticosteroid therapy, or vitreous surgery) in the study eye were censored. Missing data after censoring were imputed using the last observation prior to receiving the relevant treatment.

e) In the analysis, 53 subjects in the brolucizumab group and 52 subjects in the PRP group in whom DRSS data were missing or the severity was ungradable at all time points after baseline through Week 54, were excluded from the FAS.

f) Subjects who received alternative treatment other than the study treatment for DR or treatment relevant to DME (VEGF inhibitors other than the study treatment, periocular or intraocular corticosteroid therapy, or grid and focal laser photocoagulation) in the study eye were considered subjects in whom DME involving the central fovea was observed.

g) In the analysis, 1 subject in the PRP group in whom CSFT data were missing at all time points after baseline through Week 54 was excluded from the FAS.

h) In the analysis, 65 subjects in the brolucizumab group and 63 subjects in the PRP group in whom DRSS data were missing or the severity was ungradable at baseline, or DRSS data were missing or the severity was ungradable at all time points after baseline through Week 54, were excluded from the FAS.

Figure 2 shows the time course of the change from baseline in BCVA up to Week 96. The change from baseline in BCVA decreased over time in the PRP group, whereas in the brolucizumab group, the change was generally maintained even after Week 54. Table 6 shows the results of the main efficacy endpoints at Week 96. For all of these endpoints, the efficacy of brolucizumab was maintained up to Week 96.

Table 6. Results of efficacy endpoints at Week 96 (Study D2301, FAS)

	Brolucizumab	PRP	Between-group difference [95% CI][a)]
Change from baseline in BCVA at Week 96 (letters)[b)]	−0.5 ± 0.85 (342)	−6.4 ± 0.85 (337)	5.8 [3.5, 8.2]
Proportion of subjects in whom PDR was not observed at Week 96[c) d) e) f)]	60.6 (188/310)	28.4 (86/303)	31.9 [24.6, 39.1]
Proportion of subjects in whom DME involving the central fovea was observed by Week 96[d) g) h)]	36.3 (126/347)	76.8 (262/341)	−40.2 [−47.0, −33.3]
Proportion of subjects with a ≥2- step improvement from baseline in DRSS at Week 96[d) e) i)]	41.7 (123/295)	22.5 (65/289)	21.0 [14.3, 27.8]
Proportion of subjects with a ≥3- step improvement from baseline in DRSS at Week 96[d) e) i)]	16.6 (49/295)	11.4 (33/289)	5.6 [1.2, 10.0]

a) Brolucizumab group - PRP group
b) The data in each group are expressed as the least squares mean ± standard error (number of subjects evaluated). The analytical method is the same as that of the primary analysis. In the analysis, 5 subjects in the brolucizumab group and 5 subjects in the PRP group with missing data of the DR severity grade at baseline, one of the covariates in the primary analysis model, were excluded from the FAS.
c) Subjects with DRSS score ≥61 were classified as PDR.
d) The data in each group are expressed as % (number of applicable subjects/number of subjects evaluated). The between-group difference was calculated by the Mantel-Haenszel method with the following stratification factors: centrally-assessed DR severity grade at baseline based on DRSS (NPDR, mild or moderate PDR, high-risk PDR or more severe, ungradable), age (<55 years, ≥55 years), and region (US and Canada, East Asia, or other regions). The 95% CI for the difference was calculated based on the normal approximation to the binomial distribution. Missing values were imputed using the last observed value by the LOCF method.
e) Subjects who received alternative treatment other than the study treatment for DR or treatment relevant to DME (VEGF inhibitors and PRP other than the study treatment, periocular or intraocular corticosteroid therapy, or vitreous surgery) in the study eye were censored. Missing data after censoring were imputed using the last observation prior to receiving the relevant treatment.
f) In the analysis, 37 subjects in the brolucizumab group and 39 subjects in the PRP group in whom DRSS data were missing or the severity was ungradable at all time points after baseline through Week 96 were excluded from the FAS.
g) Subjects who received alternative treatment other than the study treatment for DR or treatment relevant to DME (VEGF inhibitors other than the study treatment, periocular or intraocular corticosteroid therapy, or grid and focal laser photocoagulation) in the study eye were considered subjects in whom DME involving the central fovea was observed.
h) In the analysis, 1 subject in the PRP group in whom CSFT data were missing at all time points after baseline through Week 96 was excluded from the FAS.
i) In the analysis, 52 subjects in the brolucizumab group and 53 subjects in the PRP group in whom DRSS data were missing or the severity was ungradable at baseline, or DRSS data were missing or the severity was ungradable at all time points after baseline through Week 96, were excluded from the FAS.

Table 7 shows the results of the primary endpoint and main secondary endpoints in the Japanese population. The results in the Japanese population tended to be similar to those in the overall population.

Table 7. Results of the primary endpoint and main secondary endpoints in the Japanese population and the overall population (Study D2301, FAS)

	Japanese			Overall		
	Brolucizumab	PRP	Between-group difference [95%CI][a)]	Brolucizumab	PRP	Between-group difference [95% CI][a)]
Primary endpoint						
Change from baseline in BCVA at Week 54 (letters)[b)]	1.3 ± 3.5 (21)	−9.7 ± 2.9 (29)	11.0 [1.7, 20.4]	0.2 ± 0.72 (342)	−4.2 ± 0.73 (337)	4.4 [2.4, 6.4]
Main secondary endpoints						
Proportion of subjects in whom PDR was not observed at Week 54[c) d) e)]	81.0 (17/21)	25.9 (7/27)	56.8 [33.8, 79.9]	63.8 (187/293)	22.4 (65/290)	39.4 [32.0, 46.8]
Proportion of subjects in whom DME involving the central fovea was observed by Week 54[d) f)]	47.6 (10/21)	89.7 (26/29)	−43.6 [−68.2, −19.1]	31.1 (108/347)	72.7 (248/341)	−41.1 [−48.0, −34.2]

a) Brolucizumab group - PRP group
b) The data in each group are expressed as the least squares mean ± standard error (number of subjects evaluated). The analytical method is the same as that of the primary analysis.
c) Subjects with DRSS score ≥61 were classified as PDR.
d) The data in each group are expressed as % (number of applicable subjects/number of subjects evaluated). The between-group difference was calculated by the Mantel-Haenszel method with the following stratification factors: centrally-assessed DR severity grade at baseline based on DRSS (NPDR, mild or moderate PDR, high-risk or worse PDR, ungradable), age (<55 years, ≥55 years), and region (US and Canada, East Asia, or other regions). The 95% CI for the difference was calculated based on the normal approximation to the binomial distribution. Missing values were imputed using the last observed value by the LOCF method.
e) Subjects who received alternative treatment other than the study treatment for DR or treatment relevant to DME (VEGF inhibitors and PRP other than the study treatment, periocular or intraocular corticosteroid therapy, or vitreous surgery) in the study eye were censored. Missing data after censoring were imputed using the last observation prior to receiving the relevant treatment.
f) Subjects who received alternative treatment other than the study treatment for DR or treatment relevant to DME (VEGF inhibitors other than the study treatment, periocular or intraocular corticosteroid therapy, or grid and focal laser photocoagulation) in the study eye were considered subjects in whom DME involving the central fovea was observed.

Table 8 shows the results of subgroup analysis of the primary endpoint by patient characteristics. No notable differences in efficacy were observed among subgroups defined by specific baseline characteristics.

Table 8. Change from baseline in BCVA at Week 54 by patient characteristics (letters) (Study D2301, FAS, LOCF)

Patient characteristic factor		Brolucizumab	PRP	Between-group difference [95% CI][a)]
Age	<55 years	1.2 ± 1.03 (174)	−4.4 ± 1.10 (153)	5.7 [2.7, 8.6]
	≥55 years	−0.7 ± 1.01 (168)	−4.1 ± 0.96 (184)	3.4 [0.6, 6.1]
Sex	Male	0.8 ± 0.99 (200)	−4.9 ± 0.97 (206)	5.7 [3.0, 8.4]
	Female	−0.5 ± 1.06 (142)	−3.0 ± 1.10 (131)	2.5 [−0.5, 5.5]
BCVA at baseline	≤75 letters	1.9 ± 1.43 (129)	−2.4 ± 1.58 (106)	4.3 [0.1, 8.5]
	>75 letters	−0.6 ± 0.81 (213)	−5.2 ± 0.78 (231)	4.6 [2.4, 6.9]
Diabetic type	Type 1	−0.9 ± 1.88 (38)	−1.8 ± 1.96 (35)	0.9 [−4.7, 6.5]
	Type 2	0.3 ± 0.78 (304)	−4.4 ± 0.79 (302)	4.8 [2.6, 6.9]
HbA1c[b)]	<7.5%	−0.2 ± 1.05 (124)	−2.4 ± 1.11 (111)	2.2 [−0.8, 5.2]
	≥7.5%	0.5 ± 0.96 (218)	−5.1 ± 0.95 (225)	5.6 [2.9, 8.2]
DR severity at baseline[c)]	NPDR[d)]	1.6 ± 1.57 (56)	−0.4 ± 1.76 (45)	2.0 [−2.8, 6.7]
	Mild or moderate PDR	−0.2 ± 0.98 (179)	−4.2 ± 0.95 (187)	4.0 [1.3, 6.7]
	High-risk or worse PDR	0.8 ± 1.59 (84)	−6.2 ± 1.53 (91)	7.0 [2.6, 11.3]
	Ungradable	0.4 ± 3.16 (23)	−5.7 ± 4.09 (14)	6.2 [−4.6, 16.9]
CSFT at baseline[e)]	<280 μm	0.0 ± 0.88 (207)	−3.2 ± 0.92 (190)	3.3 [0.8, 5.8]
	≥280 μm	0.6 ± 1.25 (135)	−5.5 ± 1.20 (146)	6.1 [2.6, 9.5]

The data in each group are expressed as the least squares mean ± standard error (number of subjects evaluated). The analytical method is the same as that of the primary analysis, except that the subgroup factor was excluded from the covariates when subgroup analyses were performed for factors included as covariates in the analysis model.

a) Brolucizumab group - PRP group
b) One subject in the PRP group in whom HbA1c data were missing at baseline was excluded from the analysis.
c) DR severity at baseline was classified based on the centrally-assessed DRSS as follows: NPDR (DRSS score ≤53), mild or moderate PDR (DRSS scores of 61 or 65), and high-risk or worse PDR (DRSS score ≥71).
d) All subjects who were classified as NPDR by the central assessment were confirmed by the investigator to have PDR in the study eye and were therefore not considered to have deviated from the inclusion criteria.
e) One subject in the PRP group in whom CSFT data were missing at baseline was excluded from the analysis.

In view of the above, the efficacy of brolucizumab in PDR patients was demonstrated.

PMDA's view:

There are no particular problems with the design of Study D2301. Taken together with the following results of Study D2301, the efficacy of brolucizumab in PDR patients is considered to have been demonstrated:

- The non-inferiority of brolucizumab to PRP was demonstrated in terms of the primary endpoint, and the results of secondary endpoints supported the results of the primary endpoint. In addition, there were no clear differences in the results of the primary endpoint or main secondary endpoints between the Japanese population and the overall population.
- From the viewpoint of the long-term efficacy of brolucizumab, the change from baseline in BCVA in the brolucizumab group was generally maintained up to Week 96, and the efficacy of brolucizumab in terms of other efficacy endpoints was also maintained up to Week 96.

7.R.2 Safety

On the basis of the clinical study results submitted in the present application and the review results presented in the following Section 7.R.2.1, PMDA has concluded that the safety of brolucizumab is acceptable, although attention should be paid during treatment with brolucizumab in PDR patients, particularly to the possibility of intraocular inflammation, endophthalmitis, retinal vasculitis and retinal vascular occlusion, intraocular pressure increased, retinal detachment and retinal tear, and arterial thromboembolic events, as in patients with the approved indications of nAMD and DME, as well as to vitreous hemorrhage, provided that brolucizumab is used only by ophthalmologists with specialized expertise in retinal diseases and adequate knowledge of and

experience in intravitreal injection procedures, and that appropriate precautionary statements regarding these events are provided.

7.R.2.1 Safety profile of brolucizumab

The applicant's explanation about the safety profile of brolucizumab in PDR patients:

Table 9 shows the incidences of adverse events in the study eye in the global phase III study (Study D2301). Although the incidence of serious adverse events assessed as related to the study treatment tended to be higher in the brolucizumab group than in the PRP group, the events observed in the brolucizumab group were uveitis, retinal occlusive vasculitis, and vitreous haemorrhage (2 subjects each), and uveitis/retinal vasculitis and endophthalmitis (1 subject each), all of which were known events during treatment with brolucizumab in patients with the approved indications of nAMD and DME. The incidences of adverse events in the study eye during treatment with brolucizumab in PDR patients in Study D2301 were also compared with those in the pooled data of the brolucizumab groups[13)] in the phase III studies of brolucizumab in nAMD patients (Studies C001 and C002) and those in the pooled data of the brolucizumab groups[13)] in the phase III studies of brolucizumab in DME patients (Studies CRTH258B2301 and CRTH258B2302 [hereinafter referred to as "Study B2301" and "Study B2302," respectively). The results showed that the incidence of vitreous haemorrhage tended to be higher in PDR patients; however, vitreous haemorrhage was considered to be related to symptoms of the primary disease, and its incidence was lower than that in the PRP group in Study D2301. Most events of vitreous haemorrhage observed in the brolucizumab group in Study D2301 were mild or moderate in severity. Among the 7 subjects with vitreous haemorrhage assessed as related to the study treatment, the events in 2 subjects were serious; however, both events resolved following vitreous surgery. The incidence of other adverse events in the study eye showed no clear differences across diseases.

[13)] Data from the brolucizumab 6 mg groups were combined.

Table 9. Incidences of adverse events in the study eye (safety analysis set)

	Study D2301		Pooled brolucizumab group in nAMD patients[a)]	Pooled brolucizumab group in DME patients[b)]
	PRP	Brolucizumab		
Number of subjects evaluated	342	347	730	368
Total exposure duration (person-years)	-	586.30	1272.66	645.18
All adverse events	199 (58.2)	152 (43.8) 46.73	394 (54.0) 81.09	165 (44.8) 55.33
Serious adverse events	30 (8.8)	13 (3.7) 2.56	25 (3.4) 2.28	12 (3.3) 2.79
Adverse events leading to discontinuation of the study treatment	40 (11.7)	16 (4.6) 2.73	24 (3.3) 1.96	8 (2.2) 1.24
Adverse events assessed as related to the study treatment	33 (9.6)	28 (8.1) 6.65	54 (7.4) 6.60	13 (3.5) 5.27
Serious adverse events assessed as related to the study treatment	2 (0.6)	8 (2.3) 1.54	13 (2.8) 1.26	3 (0.8) 0.62
Adverse events leading to discontinuation of the study treatment assessed as related to the study treatment	3 (0.9)	12 (3.5) 2.05	16 (2.2) 1.34	5 (1.4) 0.77
Main adverse events (observed in ≥3% of subjects in the brolucizumab group of Study D2301)				
Vitreous haemorrhage	83 (24.3)	38 (11.0) 7.68	2 (0.3) 0.24	6 (1.6) 0.93
Cataract	27 (7.9)	26 (7.5) 4.61	31 (4.2) 2.44	28 (7.6) 4.65
Dry eye	8 (2.3)	15 (4.3) 2.56	29 (4.0) 2.67	15 (4.1) 2.32
Intraocular pressure increased	3 (0.9)	12 (3.5) 2.22	27 (3.7) 3.06	17 (4.6) 3.87

The data in the PRP group are expressed as the number of subjects with events (incidence [%]); -, not calculated.
The data in the brolucizumab group are expressed as the number of subjects with events (incidence [%]) in the upper row, and as the number of events per 100 person-years adjusted for the total exposure duration in the lower row.
a) Results of the pooled analysis of the brolucizumab 6 mg groups in Studies C001 and C002
b) Results of the pooled analysis of the brolucizumab 6 mg groups in Studies B2301 and B2302

Table 10 shows the incidences of adverse events related to the important identified risks specified in the risk management plan (RMP) of brolucizumab, namely, intraocular inflammation,[14)] endophthalmitis,[15)] retinal vascular occlusion,[16)] intraocular pressure increased,[17)] retinal detachment and retinal tear,[18)] and retinal pigment epithelial tear,[19)] in the brolucizumab group in Study D2301. Of the serious adverse events, uveitis in 3 subjects, retinal occlusive vasculitis in 2 subjects, retinal vasculitis in 1 subject, and endophthalmitis in 1 subject were assessed as related to the study treatment, and uveitis and retinal occlusive vasculitis in 2 subjects each led to discontinuation of treatment with brolucizumab; however, all of these events resolved. The incidence of adverse events related to intraocular inflammation, endophthalmitis, retinal vascular occlusion, retinal detachment, and retinal tear in Study D2301 showed no clear differences from the incidence of the corresponding events in the pooled brolucizumab group in the phase III studies of brolucizumab in nAMD patients (Studies C001 and C002) and that in the pooled brolucizumab group in the phase III studies of

14) Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) "anterior chamber cell," "anterior chamber flare," "anterior chamber inflammation," "chorioretinitis," "choroiditis," "cyclitis," "eye inflammation," "hypopyon," "iridocyclitis," "iritis," "keratic precipitates," "keratouveitis," "necrotising retinitis," "noninfective chorioretinitis," "noninfective retinitis," "ocular vasculitis," "optic nerve disorder," "optic neuritis," "papillitis," "retinal occlusive vasculitis," "retinal vasculitis," "retinitis," "toxic anterior segment syndrome," "uveitis," "uveitis-glaucoma-hyphaema syndrome," "vitreous opacities," and "vitritis"
15) MedDRA PTs "candida endophthalmitis," "endophthalmitis," "mycotic endophthalmitis," "non-infectious endophthalmitis," "panophthalmitis," and "pseudoendophthalmitis"
16) MedDRA PTs "choroidal infarction," "eye infarction," "macular ischaemia," "ocular ischaemic syndrome," "ophthalmic vascular thrombosis," "retinal artery embolism," "retinal artery occlusion," "retinal artery stenosis," "retinal artery thrombosis," "retinal infarction," "retinal ischaemia," "retinal vascular occlusion," "retinal vascular thrombosis," "retinal vein occlusion," and "retinal vein thrombosis"
17) MedDRA PTs "intraocular pressure fluctuation," "intraocular pressure increased," "intraocular pressure test abnormal," and "ocular hypertension"
18) MedDRA PTs "macular detachment," "retinal detachment," "retinal tear," "retinopexy," "rhegmatogenous retinal detachment," "scleral buckling surgery," "serous retinal detachment," and "tractional retinal detachment"
19) MedDRA PT "retinal pigment epithelial tear"

brolucizumab in DME patients (Studies B2301 and B2302). Retinal pigment epithelial tear, which is known to occur with progression of nAMD or during treatment with VEGF inhibitors in nAMD patients (*Surv Ophthalmol*. 2017;62:493-505), was observed in the phase III studies of brolucizumab in nAMD patients, but not in the phase III studies in DME patients or Study D2301 in PDR patients.

Table 10. Incidences of adverse events in the study eye related to the important identified risks specified in the RMP (safety analysis set)

	Study D2301 Brolucizumab	Pooled brolucizumab group in nAMD patients[a)]	Pooled brolucizumab group in DME patients[b)]
Number of subjects evaluated	347	730	368
Total exposure duration (person-years)	586.30	1272.66	645.18
Intraocular inflammation	19 (5.5) 3.92	41 (5.6) 4.32	12 (3.3) 2.48
Serious adverse events	5 (1.4) 1.02	7 (1.0) 0.55	1 (0.3) 0.15
Endophthalmitis	1 (0.3) 0.17	5 (0.7) 0.39	2 (0.5) 0.31
Serious adverse events	1 (0.3) 0.17	4 (0.5) 0.31	2 (0.5) 0.31
Retinal vascular occlusion	3 (0.9) 0.68	7 (1.0) 0.55	4 (1.1) 0.77
Serious adverse events	1 (0.3) 0.34	3 (0.4) 0.24	2 (0.5) 0.31
Intraocular pressure increased	17 (4.9) 3.41	29 (4.0) 3.30	20 (5.4) 4.49
Serious adverse events	1 (0.3) 0.17	0	1 (0.3) 0.15
Retinal detachment and retinal tear	6 (1.7) 1.02	12 (1.6) 1.10	1 (0.3) 0.15
Serious adverse events	1 (0.3) 0.17	3 (0.4) 0.31	0
Retinal pigment epithelial tear	0	20 (2.7) 1.57	0
Serious adverse events	0	2 (0.3) 0.16	0

The data are expressed as the number of subjects with events (incidence [%]) in the upper row, and as the number of events per 100 person-years adjusted for the total exposure duration in the lower row.

a) Results of the pooled analysis of the brolucizumab 6 mg groups in Studies C001 and C002

b) Results of the pooled analysis of the brolucizumab 6 mg groups in Studies B2301 and B2302

Table 11 shows the incidences of non-ocular adverse events in Study D2301. No clear differences in the incidences of adverse events were observed between the brolucizumab group and the PRP group. All deaths in Study D2301 were assessed as unrelated to the study treatment. The incidences of adverse events in the brolucizumab group in Study D2301 were also compared with those in the pooled brolucizumab group from the phase III studies of brolucizumab in nAMD patients (Studies C001 and C002) and those in the pooled brolucizumab group from the phase III studies of brolucizumab in DME patients (Studies B2301 and B2302). The results showed that the incidence of hyperglycaemia and hyperkalaemia tended to be higher in the brolucizumab group in Study D2301. However, all of the events of hyperglycaemia and hyperkalaemia were assessed as unrelated to the study treatment and considered attributable to complications, and were non-serious, except in 2 subjects and 1 subject, respectively. Therefore, any specific caution regarding the development of hyperglycaemia and hyperkalaemia during treatment with brolucizumab is considered unnecessary.

Table 11. Incidences of non-ocular adverse events (safety analysis set)

	Study D2301		Pooled brolucizumab group in nAMD patients[a)]	Pooled brolucizumab group in DME patients[b)]
	PRP	Brolucizumab		
Number of subjects evaluated	342	347	730	368
Total exposure duration (person-years)	-	586.30	1272.66	645.18
All adverse events	217 (63.5) 150.61	226 (65.1) 183.00	571 (78.2) 200.41	282 (76.6)
Adverse events leading to death	9 (2.6)	8 (2.3) 1.36	12 (1.6) 0.94	21 (5.7) 3.25
Serious adverse events	64 (18.7)	62 (17.9) 20.64	154 (21.1) 19.80	101 (27.4) 30.07
Adverse events leading to discontinuation of the study treatment	1 (0.3)	2 (0.6) 0.34	13 (1.8) 1.02	12 (3.3) 2.01
Adverse events assessed as related to the study treatment	2 (0.6)	3 (0.9) 0.51	6 (0.8) 0.79	2 (0.5) 0.31
Serious adverse events assessed as related to the study treatment	0	3 (0.9) 0.51	1 (0.1) 0.08	1 (0.3) 0.15
Adverse events leading to discontinuation of the study treatment assessed as related to the study treatment	0	0	1 (0.1) 0.08	1 (0.3) 0.15
Main adverse events (observed in ≥3% of subjects in the brolucizumab group of Study D2301)				
COVID-19	47 (13.7)	44 (12.7) 7.68	0	17 (4.6) 2.63
Hypertension	24 (7.0)	35 (10.1) 6.82	52 (7.1) 4.79	35 (9.5) 6.04
Upper respiratory tract infection	16 (4.7)	28 (8.1) 5.46	24 (3.3) 2.20	10 (2.7) 1.70
Nasopharyngitis	16 (4.7)	22 (6.3) 4.09	81 (11.1) 8.64	34 (9.2) 6.82
Anaemia	15 (4.4)	15 (4.3) 2.90	12 (1.6) 0.94	18 (4.9) 3.25
Cough	10 (2.9)	15 (4.3) 2.90	25 (3.4) 2.12	16 (4.3) 2.63
Pyrexia	7 (2.0)	15 (4.3) 2.73	6 (0.8) 0.63	16 (4.3) 2.79
Hyperglycaemia	10 (2.9)	13 (3.7) 2.56	1 (0.1) 0.08	6 (1.6) 1.24
Hyperkalaemia	2 (0.6)	12 (3.5) 2.39	6 (0.8) 0.47	3 (0.8) 0.62
Urinary tract infection	13 (3.8)	12 (3.5) 2.73	43 (5.9) 4.79	26 (7.1) 5.58

The data in the PRP group are expressed as the number of subjects with events (incidence [%]); -, not calculated.
The data are expressed as the number of subjects with events (incidence [%]) in the upper row, and as the number of events per 100 person-years adjusted for the total exposure duration in the lower row.
a) Results of the pooled analysis of the brolucizumab 6 mg groups in Studies C001 and C002
b) Results of the pooled analysis of the brolucizumab 6 mg groups in Studies B2301 and B2302

Non-ocular arterial thromboembolic events,[20)] which are specified as an important potential risk in the RMP of brolucizumab, were observed in 4.6% (16 of 347) of subjects in the brolucizumab group in Study D2301. Of these, adverse events assessed as related to the study treatment were cerebral infarction in 3 subjects. These events were serious in all 3 subjects, and resolved in 2 subjects (resolved with sequelae in 1 subject) and did not resolve in 1 subject. Cerebral infarction assessed as related to brolucizumab was also reported in 1 subject in a clinical study in patients with the approved indication of nAMD. The incidence of arterial thromboembolic events, which include cerebral infarction, did not tend to greatly increase in PDR patients compared to patients with the approved indications (nAMD, 3.0% [22 of 730 subjects][21)]; DME, 5.7% [21 of 368 subjects][22)]).

[20)] MedDRA standardized MedDRA queries (SMQs) "embolic and thrombotic events, arterial" and "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous," excluding ocular events
[21)] Results of pooled analysis of the brolucizumab 6 mg group in Studies C001 and C002
[22)] Results of pooled analysis of the brolucizumab 6 mg group in Studies B2301 and B2302

Table 12 shows the incidences of adverse events in the study eye and non-ocular adverse events in the Japanese population and the non-Japanese population in Study D2301. In the brolucizumab group, no tendency toward a higher incidence of adverse events was observed in the Japanese population than in the non-Japanese population.

Table 12. Incidences of adverse events in the Japanese population and the non-Japanese population in the brolucizumab group (Study D2301, safety analysis set)

	Brolucizumab		PRP	
	Japanese	Non-Japanese	Japanese	Non-Japanese
Number of subjects evaluated	21	326	29	313
Study eye				
All adverse events	11 (52.4)	141 (43.3)	18 (62.1)	181 (57.8)
Serious adverse events	0	13 (4.0)	6 (20.7)	24 (7.7)
Adverse events assessed as related to the study treatment	1 (4.8)	27 (8.3)	3 (10.3)	30 (9.6)
Adverse events leading to treatment discontinuation	0	16 (4.9)	4 (13.8)	36 (11.5)
Non-ocular				
All adverse events	14 (66.7)	212 (65.0)	15 (51.7)	202 (64.5)
Death	0	8 (2.5)	0	9 (2.9)
Serious adverse events other than death	1 (4.8)	55 (16.9)	4 (13.8)	55 (17.6)
Adverse events assessed as related to the study treatment	0	3 (0.9)	0	2 (0.6)

Number of subjects with events (Incidence [%])

According to the above data on the incidences of adverse events in PDR patients, the events observed in the brolucizumab group were either events related to the primary disease or known events during treatment with brolucizumab in nAMD and DME patients, and no risks specific to PDR patients were identified. The safety risk of brolucizumab can therefore be managed by taking the same safety measures as for the approved indications, including the provision of precautionary statements in the package insert.

PMDA's view:

Among the adverse events observed in Study D2301, the individual events that were observed in the brolucizumab group and assessed as related to the study treatment were events known as risks associated with brolucizumab treatment in nAMD and DME patients. The applicant's explanation that the tendency toward a higher incidence of vitreous haemorrhage in PDR patients than in nAMD and DME patients is related to symptoms of the primary disease, PDR, is understandable. However, serious vitreous haemorrhage events related to brolucizumab occurred in Study D2301. Although all of these events resolved, all required vitreous surgery. Since PDR involves retinal neovascularization, patients with PDR are at a higher risk of vitreous hemorrhage than patients with nAMD or DME. The risk of vitreous hemorrhage associated with brolucizumab treatment may further increase in cases of PDR with high disease activity, such as those involving fibrovascular proliferation. In PDR patients, the occurrence of vitreous hemorrhage may make fundus examination difficult, and delayed detection of complications requiring vitreous surgery or other interventions may lead to severe visual impairment. Attention should therefore be paid to the occurrence of vitreous hemorrhage.

In view of the above, the safety risks of brolucizumab are manageable, although attention should be paid during treatment with brolucizumab in PDR patients, particularly to the possibility of intraocular inflammation, endophthalmitis, retinal vasculitis and retinal vascular occlusion, intraocular pressure increased, retinal detachment and retinal tear, and arterial thromboembolic events, as in patients with the approved indications of nAMD and DME, as well as to vitreous hemorrhage, provided that brolucizumab is used only by ophthalmologists with specialized expertise in retinal diseases and adequate knowledge of and experience in intravitreal injection procedures, and that appropriate precautionary statements are provided for these events. In addition, although it should be noted that the number of Japanese subjects in Study D2301 was limited, no safety concerns specific to Japanese PDR patients have been suggested. The safety risks of brolucizumab are therefore manageable in Japanese PDR patients as well.

7.R.3 Clinical positioning and indications

The applicant's explanation about the clinical positioning and indications of brolucizumab:

In Japan, PRP has been used as the standard treatment for PDR; however, it has been reported that PRP causes or worsens a reduction in visual acuity, loss of peripheral vision, color blindness, and macular edema (*Arch Ophthalmol*. 2009;127:132-140, *JAMA Ophthalmol*. 2016;134:666-672). Besides PRP, vitreous surgery is available as a treatment option for PDR. Vitreous surgery is indicated for PDR with massive vitreous hemorrhage or marked tractional retinal detachment, or other severe complications (Japanese diabetic retinopathy clinical practice guideline). Since retinal neovascularization in PDR is considered to be caused by increased VEGF production under ischemic conditions resulting from the occlusion of retinal capillaries (*Nat Rev Dis Primers*. 2016;2:16012), VEGF inhibitors are expected to have a therapeutic effect on PDR. The VEGF inhibitors ranibizumab and aflibercept have been approved for the treatment of DR or PDR in Europe, the US, and other countries, whereas there are no drugs approved for PDR in Japan.

The efficacy of brolucizumab for PDR was demonstrated in the global phase III study in PDR patients (Study D2301) [see Section 7.R.1] and its safety was also considered acceptable [see Section 7.R.2]. Brolucizumab can therefore be a new treatment option for PDR.

In view of the above, the proposed indication of "proliferative diabetic retinopathy" is appropriate.

PMDA's view:

The results of Study D2301 demonstrated the efficacy of brolucizumab for PDR [see Section 7.R.1] and its safety is also considered acceptable if appropriate precautionary statements are provided [see Section 7.R.2]. Brolucizumab can therefore be positioned as a new treatment option for PDR, and there are no particular problems with the proposed indication of "proliferative diabetic retinopathy."

7.R.4 Dosage and administration

7.R.4.1 Dosage and administration for PDR

PMDA asked the applicant to explain the appropriateness of the proposed dosing regimen for PDR based on the rationale for the dosing regimen of brolucizumab in the global phase III study (Study D2301), the results of the study, and other information.

The applicant's explanation about the rationale for the dosing regimen of brolucizumab in Study D2301:
It has been reported that the efficacy of aflibercept 2 mg was demonstrated in DR patients (*Lancet*. 2017;389:2193-2203). In a clinical study of brolucizumab in nAMD patients, the non-inferiority of brolucizumab 6 mg to aflibercept 2 mg was demonstrated. The dose of brolucizumab in Study D2301 was therefore set as 6 mg.

In view of the points described below, the dosing regimen of brolucizumab in Study D2301 was set as intravitreal injection Q6W for 3 consecutive doses in the loading phase, followed by intravitreal injection Q12W up to Week 48 in the maintenance phase. To reduce the dosing frequency and extend the dosing interval, if the disease was stable after Week 48, the dosing interval of brolucizumab could be extended in increments of 6 weeks to a maximum of Q24W. Conversely, if the disease worsened, the dosing interval could be reverted to Q12W. At the scheduled study visits every 6 weeks after Week 18, additional injections of brolucizumab were allowed as needed based on the assessment of disease activity.[11)]

- Based on the clinical studies of VEGF inhibitors in PDR patients (*JAMA*. 2015;314:2137-2146, *Lancet*. 2017;389:2193-2203), a reduction in the VEGF concentration in the eye early after the start of treatment to control the disease activity was expected to maintain good visual acuity with fewer doses thereafter, which would also reduce patients' burden. Therefore, a dosing regimen consisting of the loading and maintenance phases was adopted in Study D2301.
- The dosing regimen in the loading phase of Study D2301 was established with reference to the dosing regimen in the loading phase of Study B2301 in DME patients, because PDR is considered to be pathophysiologically similar to DME. However, because PDR is primarily characterized by retinal neovascularization rather than the chronic subretinal or intraretinal fluid observed in DME, it was considered that disease activity could be controlled in patients with PDR using fewer loading doses than in patients with DME. Therefore, the dosing interval in the loading phase of Study D2301 was set as Q6W, the same as that in Study B2301 in DME patients, whereas the number of loading doses was reduced to 3 consecutive doses, compared with 5 consecutive Q6W doses in Study B2301.
- In the clinical studies of VEGF inhibitors in PDR patients (*JAMA*. 2015;314:2137-2146, *Lancet*. 2017;389:2193-2203), the number of doses was approximately 6 in the first year of treatment and approximately 2 to 3 in the second year. In view of this, the dosing interval in the maintenance phase of Study D2301 was set as Q12W, and could be further extended after Week 48 if the disease was stable. In Study D2301, based on the recommended ophthalmologic visit interval in PDR patients in Japan and the US (Japanese diabetic retinopathy clinical practice guideline; Diabetic Retinopathy Preferred Practice Pattern. American Academy of Ophthalmology; 2024), the study visits were scheduled every 6 weeks. At each scheduled visit, an additional injection of brolucizumab 6 mg was allowed if disease

activity was determined to be present based on the investigator's assessment.[11)]

The applicant's explanation about the rationale for and appropriateness of the proposed dosing regimen of brolucizumab for PDR based on the results of Study D2301 conducted using the above dosing regimen and other information:
In Study D2301, the non-inferiority of brolucizumab 6 mg to PRP was demonstrated [see Section 7.R.1] and its safety was acceptable [see Section 7.R.2]. The proposed dose of brolucizumab for PDR was therefore set as 6 mg in both the loading and maintenance phases.

Based on the results of Study D2301 shown below and other information, the dosing regimen in the loading phase is usually Q6W for 3 consecutive doses, and it is appropriate to adjust the number of brolucizumab doses in the loading phase as appropriate based on the patient's condition.

- Of the subjects who received brolucizumab Q6W for 3 consecutive doses, 9.8% (34 of 347 subjects) were determined to require an additional injection of brolucizumab based on the presence of disease activity at Week 18. Therefore, the majority of subjects could enter the maintenance phase after receiving 3 consecutive doses. It is therefore appropriate that the number of doses in the loading phase should usually be 3 consecutive doses.
- In Study D2301, administration of brolucizumab at Week 24 was specified even in subjects who received an additional injection of brolucizumab at Week 18. Accordingly, subjects who received an additional injection of brolucizumab at Week 18, excluding those in whom treatment with brolucizumab was discontinued, received brolucizumab at Week 24. In the maintenance phase after Week 24, many subjects received brolucizumab at a dosing interval of Q12W or longer. The change from baseline in BCVA at Weeks 54 and 96 in the subgroup of subjects who required Q6W treatment for ≥4 consecutive doses in the loading phase (least squares mean ± standard error) (number of subjects evaluated) was 0.5 ± 1.29 (34 subjects) and 0.1 ± 1.48 (34 subjects), respectively, which were similar to the results in the overall population of the brolucizumab group (Table 3 and Table 6). Because no differences were observed between this subgroup and the overall population of the brolucizumab group in the incidences of adverse events in the study eye or non-ocular adverse events, administration of >3 loading doses was considered acceptable.
- In Study D2301, although efficacy evaluation based on fundus examination was not performed at Weeks 6 and 12 (corresponding to the second and third doses), 41.0% (103 of 251) of subjects in the brolucizumab group achieved a ≥2-step improvement from baseline in diabetic retinopathy severity scale (DRSS) at Week 18 (6 weeks after the third dose). As shown in the time course of the change from baseline in BCVA (Figure 2), BCVA was generally maintained in the brolucizumab group at Weeks 6, 12, and 18. Since the maintenance or improvement of visual acuity and the improvement of DRSS are considered to have a certain degree of correlation, it can be inferred that the disease activity of PDR in patients whose visual acuity was stable or improved at Week 12 in Study D2301 had stabilized or improved before the administration of brolucizumab at Week 12. It was thus inferred that a certain number of subjects did not require 3 doses in the loading phase to control the disease activity of PDR. In the actual clinical setting, disease activity is considered to be assessed not only based on visual acuity

but also on fundus findings and other clinical information. Therefore, the number of doses in the loading phase may be reduced as appropriate based on the disease activity in each patient. Allowing a reduction in the number of doses in the loading phase based on the patient's condition is also considered useful from the viewpoint of reducing the burden on patients and healthcare professionals.

Based on the results of Study D2301 shown below and other information, the dosing interval in the maintenance phase should usually be Q12W, with adjustment according to disease activity and a minimum interval of 8 weeks.

- In the maintenance phase of Study D2301, the dosing interval was maintained at Q12W in 75.1% (238 of 317[23)]) of subjects up to Week 54, the primary evaluation time point, and the non-inferiority of brolucizumab to PRP was demonstrated. Therefore, the dosing interval in the maintenance phase should usually be Q12W.
- In Study D2301, the dosing interval could be extended after Week 48 based on the assessment of disease activity. Among subjects who received at least one dose of brolucizumab during the maintenance phase, 47.2% (150 of 318 subjects [Q18W, 70 subjects; Q24W or longer, 80 subjects]) had a final dosing interval longer than Q12W up to Week 96 and showed no disease activity during the period from the time of the last administration to the end of that interval. This result indicates that disease activity could be controlled with a longer dosing interval than Q12W in approximately half of the subjects. The change from baseline in BCVA at Week 96 in subgroups of subjects with a final dosing interval of Q18W and Q24W or longer (least squares mean ± standard error) (number of subjects evaluated) was 2.0 ± 0.90 (88 subjects) and 1.9 ± 0.69 (104 subjects), respectively.
- The dosing interval in the maintenance phase of Study D2301 was usually Q12W, and additional injections were allowed based on the assessment of disease activity at study visits every 6 weeks. In the maintenance phase of Study D2301, although none of the subjects required additional injections on a continuous basis through study completion, 21.6% (75 of 347 subjects) received at least 1 additional injection. It is therefore appropriate to allow shortening of the dosing interval in the maintenance phase to 12 weeks or shorter based on the patient's condition. In the approved dosing regimens of brolucizumab for the approved indications of nAMD and DME, the minimum dosing interval is specified as Q8W, and it is suggested that repeated administration of brolucizumab Q4W may increase the incidence of adverse events such as intraocular inflammation and retinal vascular occlusion (*Ophthalmology*. 2022;129:974-985). Because continuous additional dosing was not performed in Study D2301, the possibility that the incidence of adverse events may increase when the dosing interval is shortened to less than Q8W cannot be ruled out. In addition, given that patients with PDR may also have DME and that use of a dosing interval different from that for DME could cause confusion in clinical practice, the minimum dosing interval in the maintenance phase should be Q8W.

The Japanese diabetic retinopathy clinical practice guideline states that vitreous surgery is indicated for cases with tractional retinal detachment threatening the macula, tractional retinal detachment with concurrent retinal

[23)] The denominator is the number of subjects in the brolucizumab group who remained in the study through Week 54 in Study D2301.

tear, massive vitreous hemorrhage, persistent vitreous hemorrhage, etc. In view of this, if any signs of worsening of the clinical condition, such as a reduction in visual acuity, newly developed or enlarged retinal neovascularization, recurrent vitreous hemorrhage, or tractional retinal detachment, are observed despite continued treatment with brolucizumab, it is desirable to consider discontinuing the treatment and using alternative treatments such as vitreous surgery.

PMDA's view:
In Study D2301, the efficacy of brolucizumab 6 mg in PDR patients was demonstrated [see Section 7.R.1] and its safety was also acceptable [see Section 7.R.2]. Therefore, there are no problems with setting the dose of brolucizumab as 6 mg in both the loading and maintenance phases.

In Study D2301, although the dosing interval in the loading phase was set as Q6W for 3 consecutive doses, additional doses were allowed based on the assessment of disease activity. Consequently, subjects could receive ≥4 consecutive doses Q6W starting from the initial dose. However, only 9.8% (34 of 347) of subjects received ≥4 consecutive doses at Q6W intervals from the initial dose. Given that most subjects transitioned to the maintenance phase after 3 consecutive Q6W doses and that brolucizumab 6 mg demonstrated efficacy with acceptable safety, the loading regimen should usually consist of 3 consecutive doses administered at Q6W intervals. Since there were no particular concerns about the efficacy or safety of brolucizumab in subjects who received ≥4 consecutive doses Q6W from the initial dose in Study D2301, it is also appropriate to allow an increase in the number of doses in the loading phase based on the patient's condition.

With respect to reducing the number of doses in the loading phase, the applicant explained that efficacy evaluation based on fundus examination was not performed until Week 12 in Study D2301, and it could be inferred based on the results of BCVA from Weeks 6 to 18 and the results of DRSS at Week 18 that the disease activity of PDR had also stabilized or improved in patients whose visual acuity was stable or improved at Week 12. However, this explanation has limitations because visual acuity in PDR is unlikely to change substantially in the short term unless the patient has macular edema or other serious complications. However, the applicant's explanation that the number of doses required before transition to the maintenance phase may vary among patients is understandable to a certain extent. Taking into account the patients' burden associated with intravitreal injections and assuming that, in the actual clinical setting, disease activity is assessed not only based on visual acuity but also on fundus findings and other clinical information, it is acceptable to reduce the number of doses in the loading phase as appropriate based on the patient's condition.

In Study D2301, the dosing regimen in the maintenance phase was set as Q12W up to Week 48, and additional injections were allowed based on the assessment of disease activity at study visits every 6 weeks. However, 75.1% (238 of 317) of subjects did not require additional injections through Week 54, and the non-inferiority of brolucizumab to PRP was demonstrated with acceptable safety. Therefore, it is appropriate for the dosing interval of brolucizumab in the maintenance phase to usually be Q12W. The dosing interval could be extended after Week 48 in Study D2301. At Week 96, the proportions of subjects with a dosing interval of Q18W and

those with a dosing interval of Q24W or longer were 22.0% (70 of 318 subjects) and 25.2% (80 of 318 subjects), respectively. In Study D2301, some subjects received additional doses at study visits every 6 weeks; however, no subjects required continuous Q6W dosing through Week 90. Given this, and considering that the minimum dosing interval in the approved dosing regimens of brolucizumab for the approved indications (nAMD and DME) is 8 weeks based on safety considerations and other factors, the applicant's explanation that the minimum dosing interval in the maintenance phase should also be 8 weeks for PDR is understandable. In view of the above, it is possible to allow adjustment of the dosing interval based on the patient's condition and set the minimum dosing interval as 8 weeks for the dosing regimen of brolucizumab in the maintenance phase.

The Japanese diabetic retinopathy clinical practice guideline states that vitreous surgery is indicated for cases with tractional retinal detachment threatening the macula, tractional retinal detachment with concurrent retinal tear, massive vitreous hemorrhage, persistent vitreous hemorrhage, etc. It has also been reported that treatment with VEGF inhibitors in patients with fibrovascular proliferation may cause the fibrovascular membrane to contract, which may lead to tractional retinal detachment (*Surv Ophthalmol*. 2021;66:926-932). Because delays in performing vitreous surgery or other appropriate interventions may lead to further disease progression, severe visual impairment, or vision loss, it is appropriate to advise that fundus examinations and other assessments be performed regularly after administration of brolucizumab. If signs of worsening of the clinical condition of PDR, such as vitreous hemorrhage, tractional retinal detachment, or fibrovascular proliferation, are observed, continuation of brolucizumab treatment should be reconsidered, and alternative treatment such as vitreous surgery should be considered.

7.R.5 Post-marketing investigations

The applicant's explanation:

In view of the points described below, no concerns specific to PDR patients that should be further characterized in the post-marketing setting had been identified. Therefore, rather than implementing additional pharmacovigilance activities, including post-marketing surveillance in PDR patients, it is appropriate to promptly consider and implement appropriate risk minimization measures as needed based on information obtained through routine pharmacovigilance activities and to provide such information to healthcare professionals.

- In Study D2301 in PDR patients, the safety profile of brolucizumab showed a tendency toward a higher incidence of vitreous haemorrhage than that observed in patients with the approved indications of nAMD and DME. However, vitreous haemorrhage was a known event that had been reported in both nAMD and DME patients, and no clinically relevant safety risks specific to PDR patients were identified, including with respect to other events [see Section 7.R.2].
- The latest periodic safety update report (reporting period, up to October 6, 2024; estimated number of patients who used brolucizumab, approximately [redacted] person-years), as well as the specified drug use-results survey in nAMD patients conducted in Japan (Study CRTH258A1401; 329 confirmed enrolled patients and 328 patients included in the safety analysis) and the specified drug use-results survey in DME patients conducted in Japan (Study CRTH258B1401; 222 confirmed enrolled patients, all of whom were included in the safety analysis) identified no new safety concerns.

The applicant's additional explanation:

Because no new safety concerns are expected to arise from the proposed addition to the dosing regimen for nAMD [see Section 6.R.1], no additional pharmacovigilance activities, including post-marketing surveillance, will be conducted.

PMDA's view:

According to the results of Study D2301, although the incidence of vitreous haemorrhage tended to be higher in PDR patients than in patients with the approved indications, the situation of its occurrence has been clarified to a certain extent in Study D2301, and no other new safety concerns specific to PDR patients were identified [see Section 7.R.2]. In addition, no new safety concerns have been identified to date based on the latest periodic safety update report, specified drug use-results surveys in Japan, and other available data. In view of these points, there are no concerns about the use of brolucizumab in PDR patients that require further characterization after the market launch. Therefore, provided that routine pharmacovigilance activities ensure provision of relevant safety information to healthcare professionals regarding adverse events requiring particular attention during treatment with brolucizumab, collection of safety information on brolucizumab, and implementation of appropriate safety measures based on currently available and future safety information, the need for additional pharmacovigilance activities, including post-marketing surveillance in PDR patients, is considered low.

In view of the applicant's explanation, the need for additional pharmacovigilance activities, including post-marketing surveillance, in relation to the proposed addition to the dosing regimen for nAMD is considered low.

However, if new issues requiring further evaluation are identified in the post-marketing setting for brolucizumab, the applicant should immediately consider implementation of additional pharmacovigilance activities, including post-marketing surveillance.

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

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

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

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that brolucizumab has efficacy in the treatment of PDR, and that brolucizumab has acceptable safety in view of its benefits. Brolucizumab is clinically meaningful because it offers a new treatment option for PDR patients. PMDA has also concluded that it is possible to add the dosing regimen of 2 or 3 doses administered at Q6W intervals in the loading phase for the treatment of nAMD.

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

Review Report (2)

October 7, 2025

Product Submitted for Approval

Brand Name	Beovu Kit for Intravitreal Injection 120 mg/mL
Non-proprietary Name	Brolucizumab (genetical recombination)
Applicant	Novartis Pharma K.K.
Date of Application	December 12, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1. Efficacy for PDR

In view of the discussions presented in Section "7.R.1 Efficacy" in the Review Report (1), PMDA concluded that the efficacy of brolucizumab for PDR was demonstrated.

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

1.2. Safety for PDR

In view of the discussions presented in Section "7.R.2 Safety" in the Review Report (1), PMDA concluded that the safety of brolucizumab is acceptable, although attention should be paid during treatment with brolucizumab in PDR patients, particularly to the possibility of intraocular inflammation, endophthalmitis, retinal vasculitis and retinal vascular occlusion, intraocular pressure increased, retinal detachment and retinal tear, and arterial thromboembolic events, as in patients with the approved indications of nAMD and DME, as well as to vitreous hemorrhage, provided that brolucizumab is used only by ophthalmologists with specialized expertise in retinal diseases and adequate knowledge of and experience in intravitreal injection procedures, and that appropriate precautionary statements are provided for these events.

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

1.3. Clinical positioning and indication for PDR

In view of the discussions presented in Section "7.R.3 Clinical positioning and indications" in the Review Report (1), PMDA concluded that brolucizumab can be positioned as a new treatment option for PDR patients and that the proposed indication is acceptable as submitted.

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

1.4. Dosage and administration

1.4.1. Dosage and administration for nAMD

In view of the discussions presented in Section "6.R.1 Dosage and administration for nAMD" in the Review Report (1), PMDA concluded that it is possible to add the intravitreal injection of brolucizumab 6 mg Q6W for 2 consecutive doses, or 3 consecutive doses if disease activity is present, as a dosing regimen of brolucizumab in the loading phase for nAMD.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion. PMDA thus instructed the applicant to modify the dosing regimen of brolucizumab for nAMD and the "Precautions Concerning Dosage and Administration" section of the package insert as presented below. The applicant responded accordingly.

Dosage and Administration

The recommended dosage in the loading phase is 6 mg (0.05 mL) of brolucizumab (genetical recombination), administered by intravitreal injection once every 4 weeks for 3 consecutive doses. Alternatively, the same dose may be administered by intravitreal injection once every 6 weeks for 2 consecutive doses. An additional dose may be administered based on the patient's condition. Subsequently, in the maintenance phase, the same dose is administered by intravitreal injection, usually once every 12 weeks. The dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 weeks.

Precautions Concerning Dosage and Administration

If a 6-week dosing interval is used during the loading phase, disease activity should be assessed after administration of 2 consecutive doses, and if any findings suggestive of disease activity are observed, administration of a third dose should be considered. In the maintenance phase, disease activity should be periodically assessed, and if any findings suggestive of disease activity are observed, appropriate measures, including using an 8-week dosing interval, should be considered.

1.4.2. Dosage and administration for PDR

In view of the discussions presented in Section "7.R.4 Dosage and administration" in the Review Report (1), PMDA concluded that the following dosing regimen for PDR is acceptable: in the loading phase, brolucizumab 6 mg is administered by intravitreal injection every 6 weeks, usually for 3 consecutive doses, and the number of doses may be adjusted as appropriate based on the assessment of disease activity; in the maintenance phase, brolucizumab 6 mg is administered by intravitreal injection, usually every 12 weeks, and the dosing interval

may be adjusted as appropriate based on the assessment of disease activity, with a minimum dosing interval of 8 weeks. PMDA also concluded that it is appropriate to advise that fundus examinations and other assessments be performed regularly after administration of brolucizumab. If signs of worsening of the clinical condition of PDR, such as vitreous hemorrhage, tractional retinal detachment, or fibrovascular proliferation, are observed, continuation of brolucizumab treatment should be reconsidered, and alternative treatment such as vitreous surgery should be considered.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusions. PMDA thus instructed the applicant to specify the dosing regimen for PDR as proposed by the applicant and to provide the following precautionary statements in the "Precautions Concerning Dosage and Administration" section of the package insert. The applicant responded accordingly.

Precautions Concerning Dosage and Administration

- In the loading phase, the number of doses may be reduced to fewer than 3 or increased by administering additional doses based on the assessment of disease activity. In the maintenance phase, disease activity should be periodically assessed, and if any findings suggestive of disease activity are observed, appropriate measures, including using an 8-week dosing interval, should be considered.
- Fundus examinations and other assessments should be performed regularly after administration of brolucizumab. If signs of worsening of the clinical condition of proliferative diabetic retinopathy, such as vitreous hemorrhage, tractional retinal detachment, or fibrovascular proliferation, are observed, continuation of brolucizumab treatment should be reconsidered, and alternative treatment such as panretinal photocoagulation and vitreous surgery should be considered.

1.5. Risk management plan (draft)

In view of the discussions presented in Section "7.R.5 Post-marketing investigations" in the Review Report (1), PMDA concluded that there is little need to conduct additional pharmacovigilance activities including post-marketing surveillance in PDR patients after the market launch of brolucizumab, and that there is also little need to conduct additional pharmacovigilance activities including post-marketing surveillance for the additional dosing regimen for nAMD either.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion. PMDA concluded that it is appropriate to include the safety specification presented in Table 13 in the current RMP (draft) for brolucizumab, and to conduct the additional pharmacovigilance and risk minimization activities presented in Table 14.

Table 13. Safety and efficacy specifications in the risk management plan (draft)[a)]

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Intraocular inflammation • Endophthalmitis • Intraocular pressure increased • Retinal pigment epithelial tear • Retinal detachment and retinal tear • Retinal vasculitis and retinal vascular occlusion • ~~Retinal arterial embolic events~~	• Non-ocular arterial thromboembolic events	• Not applicable
Efficacy specification		
• Not applicable		

a) No items were added for the present application. "Retinal arterial embolic events," which had been specified as an important identified risk at the time of the previous approval, are included in "retinal vasculitis and retinal vascular occlusion" because these events are classified under the heading of "retinal vasculitis and retinal vascular occlusion."

(Strikethrough denotes deletion.)

Table 14. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)[a)]

Additional pharmacovigilance activities	Additional risk minimization activities
• Not applicable	• Preparation and distribution of materials for healthcare professionals • Preparation and distribution of materials for patients

a) Information relevant to the present application is presented.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indications and dosage and administration revised as described below, under the following approval condition. The re-examination period for the present application is the remainder of the current re-examination period for the initial approval of the product (until March 24, 2028).

Indications

○ Age-related macular degeneration with subfoveal choroidal neovascularization

○ Diabetic macular edema

○ <u>Proliferative diabetic retinopathy</u>

(Underline denotes additions.)

Dosage and Administration

Age-related macular degeneration with subfoveal choroidal neovascularization

The recommended dosage <u>in the loading phase</u> is 6 mg (0.05 mL) of brolucizumab (genetical recombination), administered by intravitreal injection once every 4 weeks for 3 consecutive doses ~~(loading phase)~~. <u>Alternatively, the same dose may be administered by intravitreal injection once every 6 weeks for 2 consecutive doses. An additional dose may be administered based on the patient's condition.</u> Subsequently, in the maintenance phase, the same dose is administered by intravitreal injection, usually once every 12 weeks. The dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 weeks.

Diabetic macular edema

The recommended dosage is 6 mg (0.05 mL) of brolucizumab (genetical recombination), administered by intravitreal injection once every 6 weeks, usually for 5 consecutive doses (loading phase). The number of doses may be reduced as appropriate based on the patient's condition. Subsequently, in the maintenance phase, the same dose is administered by intravitreal injection, usually once every 12 weeks. The dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 weeks.

Proliferative diabetic retinopathy

The recommended dosage is 6 mg (0.05 mL) of brolucizumab (genetical recombination), administered by intravitreal injection once every 6 weeks, usually for 3 consecutive doses (loading phase). The number of doses may be adjusted as appropriate based on the patient's condition. Subsequently, in the maintenance phase, the same dose is administered by intravitreal injection, usually once every 12 weeks. The dosing interval may be adjusted as appropriate based on the patient's condition, with a minimum interval of 8 weeks.

(Underline denotes additions, and strikethrough denotes deletions.)

Approval Condition

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

Appendix

List of Abbreviations

Aflibercept	Aflibercept (genetical recombination)
BCVA	Best-corrected visual acuity
Beovu	Beovu Kit for Intravitreal Injection 120 mg/mL
Brolucizumab	Brolucizumab (genetical recombination)
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSFT	Central subfield thickness
CTD	Common technical document
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic retinopathy severity scale
ETDRS	Early treatment diabetic retinopathy study
FAS	Full analysis set
HbA1c	Hemoglobin A1c
Japanese diabetic retinopathy clinical practice guideline	Diabetic Retinopathy Clinical Practice Guidelines (First Edition). *Journal of Japanese Ophthalmological Society*. 2020;124:955-981
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	Neovascular age-related macular degeneration
NPDR	Non-proliferative diabetic retinopathy
PD	Pharmacodynamics
PDR	Proliferative diabetic retinopathy
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PRP	Panretinal photocoagulation
PT	Preferred term
QxW	Once every x weeks
Ranibizumab	Ranibizumab (genetical recombination)
RMP	Risk management plan
SMQ	Standardized MedDRA query
Study B2301	Study CRTH258B2301
Study B2302	Study CRTH258B2302
Study C001	Study RTH258-C001
Study C002	Study RTH258-C002
Study D2301	Study CRTH258D2301
Study E003	Study RTH258-E003
VEGF	Vascular endothelial growth factor