Information Meeting on Vabysmo®

CHUGAI PHARMACEUTICAL CO., LTD.

24 June 2022

Agenda

01 **Overview of Vabysmo® Solution for Intravitreal Injection 120 mg/mL**

Vabysmo Lifecycle Leader,
Chugai Pharmaceutical Co., Ltd.
Masashi Kishida, Ph.D.

02 **Clinical Significance of Vabysmo®**

Professor & Chairman, Department of Ophthalmology,
Tokyo Women's Medical University
Tomohiro Iida, M.D., Ph.D.

03 **Q&A**

Overview of Vabysmo® Solution for Intravitreal Injection 120 mg/mL

Standard Commodity Classification Number of Japan	871319

Ophthalmic VEGF[Note 1]/Ang-2[Note 2] inhibitor
Anti-VEGF/anti-Ang-2 humanized bispecific monoclonal antibody
Biological product/powerful drug/prescription-only drug[Note 3] Listed on the NHI Drug Price List

Vabysmo®

Solution for Intravitreal Injection 120 mg/mL

VABYSMO® Solution for Intravitreal Injection

Faricimab (genetical recombination) solution for intravitreal injection

Note 1 VEGF: vascular endothelial growth factor
Note 2 Ang-2: Angiopoietin-2
Note 3 Use only pursuant to a prescription by a physician, etc.

Newly Launched

Masashi Kishida
Vabysmo Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.

Features of Vabysmo

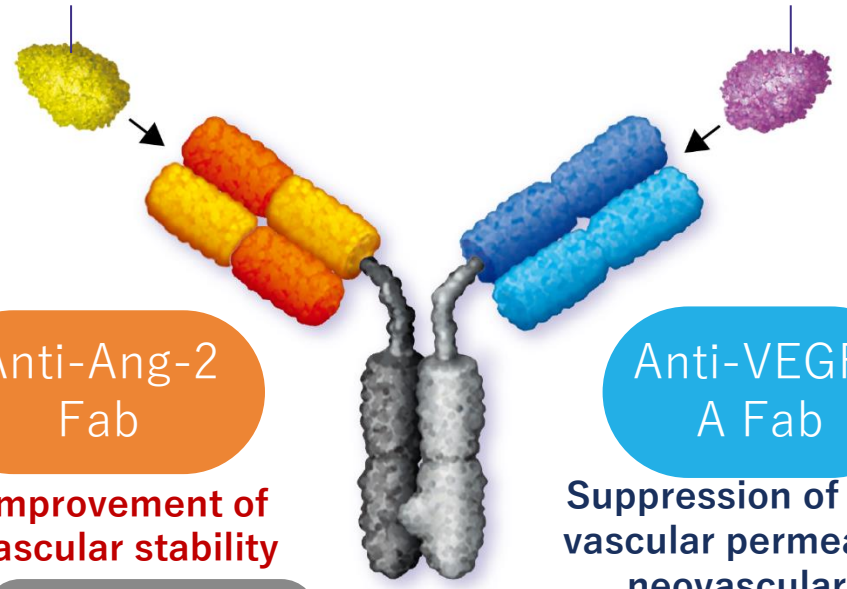
The first bispecific antibody in ophthalmology, specifically binding to VEGF-A and Ang-2

V A BYSMO

VEGF-A | Ang-2 | Bispecific | Molecule

Ang-2 (angiopoietin-2)

VEGF-A
(vascular endothelial growth factor-A)



Anti-Ang-2 Fab

Improvement of vascular stability

Modified Fc

Anti-VEGF-A Fab

Suppression of increased vascular permeability and neovascularization

(conceptual illustration)

- Decrease in systemic exposure
- Reduction in proinflammatory effect

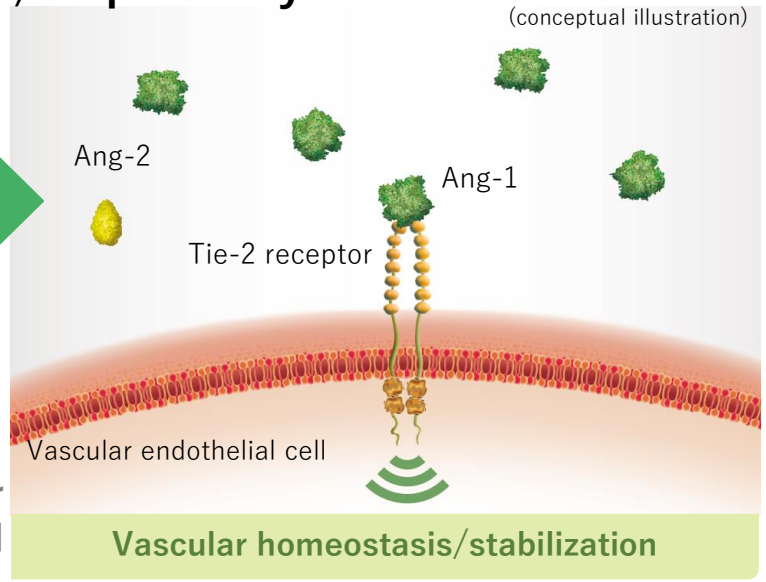
Evaluation material for approval: binding affinity of faricimab to the target

https://pubmed.ncbi.nlm.nih.gov/27742718/ [Internet; cited May 2022]

Mechanisms of Vascular Stabilization and Destabilization

VEGF-A, Ang-1, and Ang-2 affect inflammation and neovascularization, vascular stabilization, and vascular destabilization, respectively

Action of Ang-1 as vascular stabilization factor



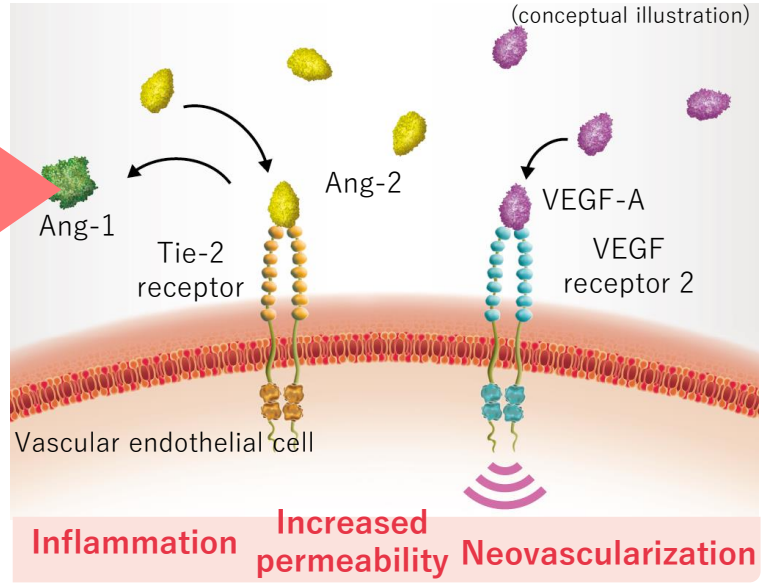
Normal vascular endothelial cell

Vascular homeostasis/stabilization

Coordination between Ang-2, a vascular destabilization factor, and VEGF-A

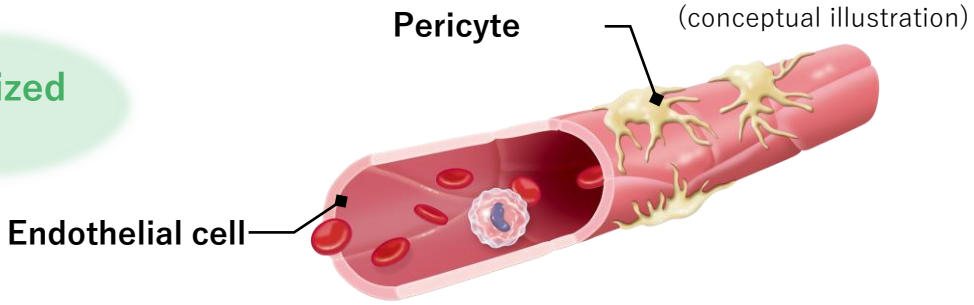
nAMD

DME

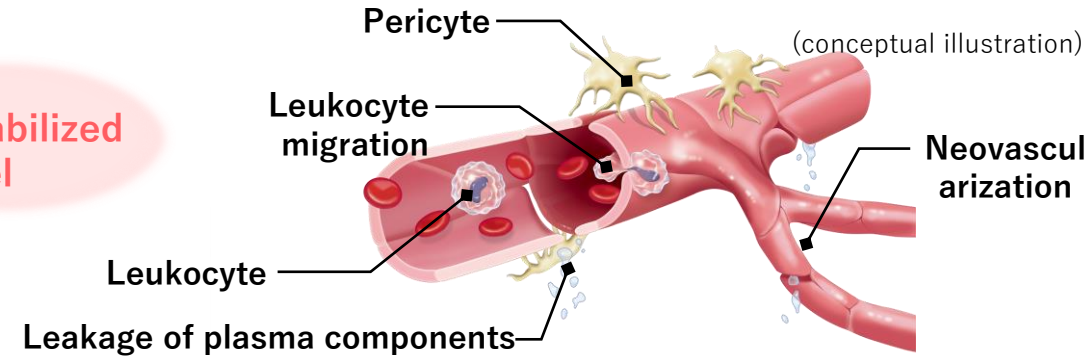


Inflammation **Increased permeability** **Neovascularization**

Stabilized vessel



Destabilized vessel



Ang-1: angiopoietin-1, Ang-2: angiopoietin-2, VEGF: vascular endothelial growth factor, nAMD: neovascular age-related macular degeneration, DME: diabetic macular edema

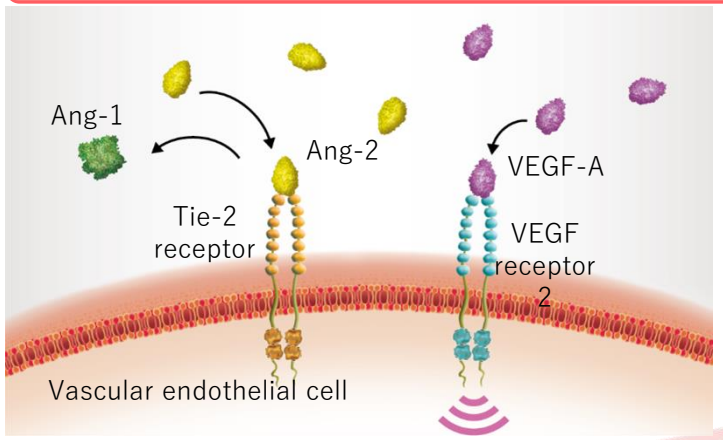
1) Ichinose, A. (Ed.). Thrombosis, Hemostasis, and Vascular Sciences. 2005, P36-37. CHUGAI-IGAKUSHA.; 2) Lee J, et al. Invest Ophthalmol Vis Sci. 2014;55(4):2191–9.; 3) Regula JT, et al. EMBO Mol Med. 2016;8(11):1265-88. with correction in Regula JT, et al. EMBO Mol Med. 2019;11(5):e10666. (conflict of interest: Employees of Roche Ltd. [at the time of experiment], Roche Diagnostics GmbH, and F. Hoffmann-La Roche Ltd. are included in the authors) 4)Hammes HP, et al. Diebetes. 2004;53(4):1104-10. 5) Aiello LP, et al. N Engl J Med. 1994; 331(22):1480-7. 6)Benest AV, et al. PLoS One. 2013;8(8):e70459. 7)Oshima Y, et al. J Cell Physiol. 2004;199(3):412-7. 8)Peters S, et al. Cytokine. 2007;40(2):144-50. 9)Oh H, et al. J Biol Chem. 1999;274:15732-9. 10)Rangasamy S, et al. Invest Ophthalmol Vis Sci. 2011;52:3784-91.

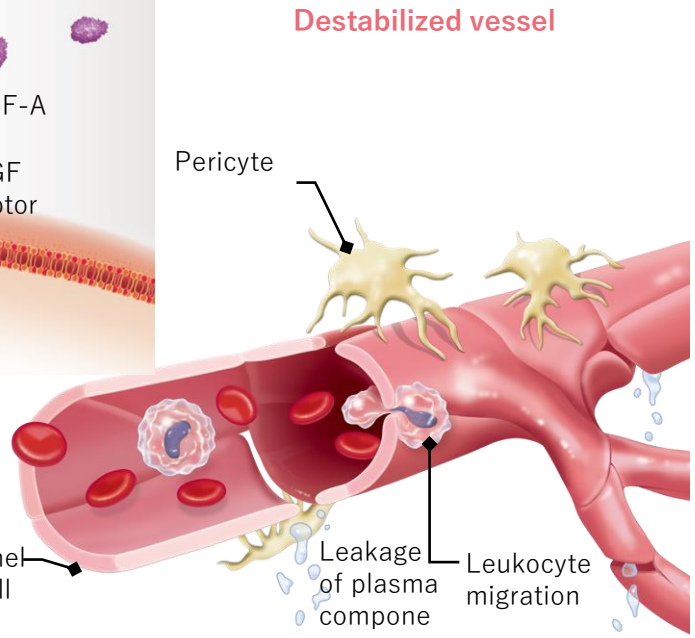
Action Mechanism of Vabysmo

Vabysmo, which inhibits VEGF-A and Ang-2 at the same time by one molecule, has been expected to exert the two effects below:

- **Inhibitory effects against Ang-2: mainly include suppression of vascular destabilization by pericyte deficit, increased vascular permeability, and increased sensitivity to VEGF-A**
- **Inhibitory effects against VEGF-A: mainly include suppression of increased vascular permeability, neovascularization, and inflammation**

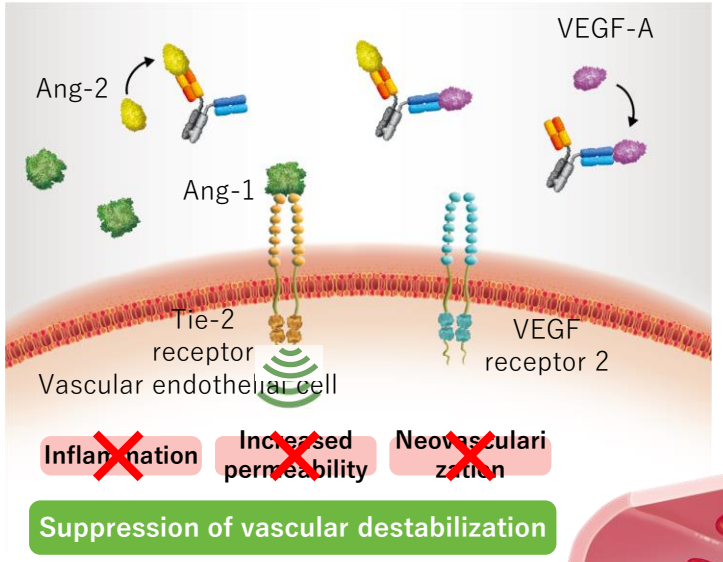
Coordination between VEGF-A and Ang-2





(conceptual illustration)

Action of Vabysmo



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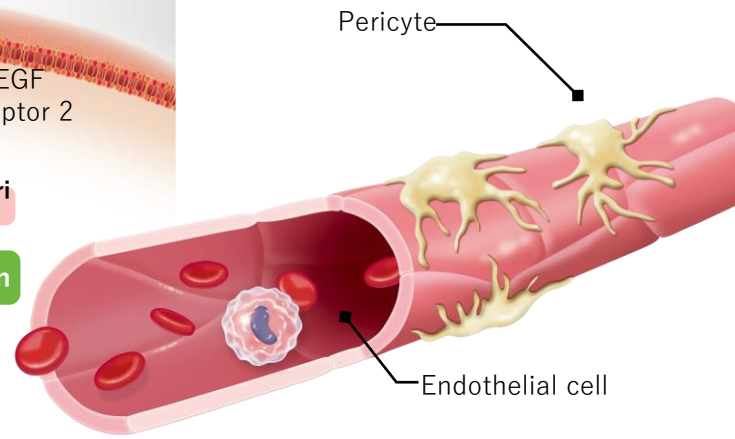
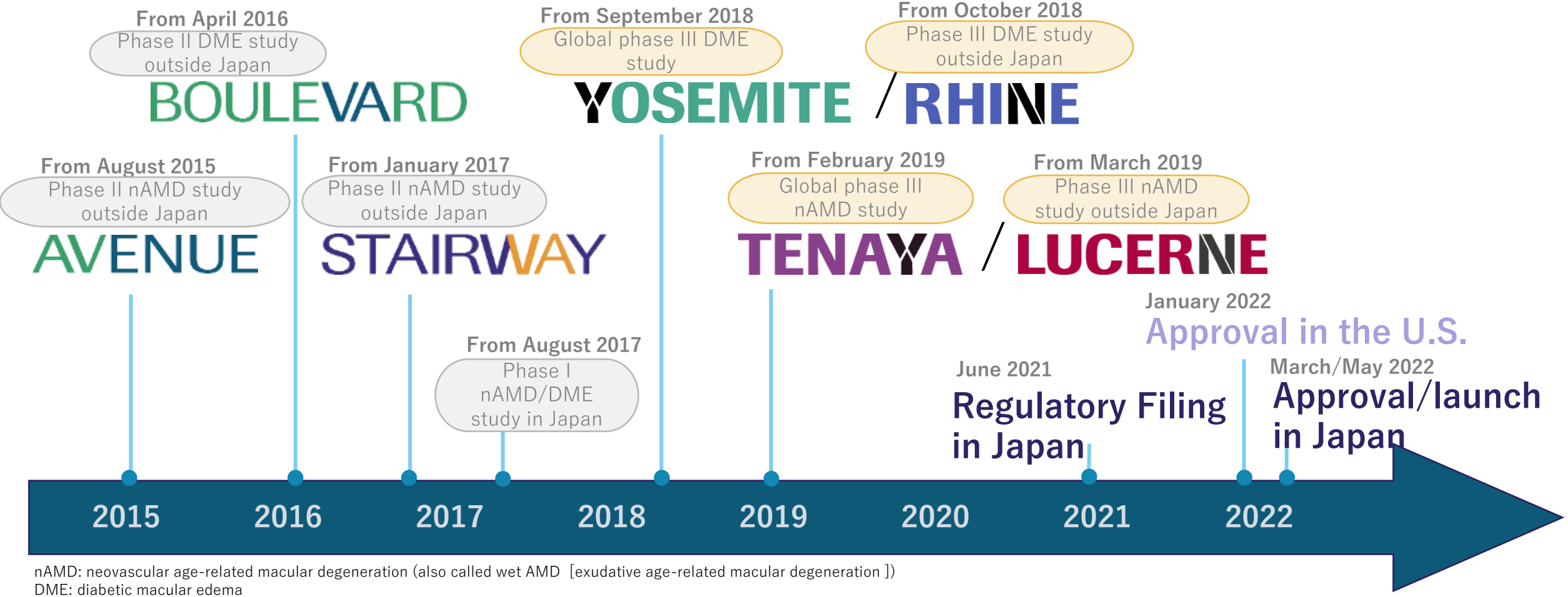


VEGF-A: vascular endothelial growth factor-A, Ang-2: angiopoietin-2, Ang-1: angiopoietin-1

1) Ichinose, A. (Ed.). Thrombosis, Hemostasis, and Vascular Sciences. 2005, P36-37. CHUGAI-IGAKUSHA.; 2) Lee J, et al. Invest Ophthalmol Vis Sci. 2014;55(4):2191–9.; 3) Regula JT, et al. EMBO Mol Med. 2016;8(11):1265-88. with correction in Regula JT, et al. EMBO Mol Med. 2019;11(5):e10666. (conflict of interest: Employees of Roche Ltd. [at the time of experiment], Roche Diagnostics GmbH, and F. Hoffmann-La Roche Ltd. are included in the authors) 4)Hammes HP, et al. Diebetes. 2004;53(4):1104-10. 5) Aiello LP, et al. N Engl J Med. 1994; 331(22):1480-7. 6)Benest AV, et al. PLoS One. 2013;8(8):e70459. 7)Oshima Y, et al. J Cell Physiol. 2004;199(3):412-7. 8)Peters S, et al. Cytokine. 2007;40(2):144-50. 9)Oh H, et al. J Biol Chem. 1999;274:15732-9. 10)Rangasamy S, et al. Invest Ophthalmol Vis Sci. 2011;52:3784-91.

Development History of Vabysmo

Vabysmo has been developed for two indications of age-related macular degeneration associated with subfoveal choroidal neovascularization and diabetic macular edema. In March 2022, those indications were approved at the same time in Japan (the second country worldwide after the United States).



nAMD: neovascular age-related macular degeneration (also called wet AMD [exudative age-related macular degeneration])
DME: diabetic macular edema

Characteristics of Vabysmo Solution for Intravitreal Injection

1. Vabysmo is thought to stabilize the vessels and exert effects by inhibiting VEGF-A and Ang-2 simultaneously. VEGF-A causes pathological neovascularization and increased vascular permeability in age-related macular degeneration associated with subfoveal choroidal neovascularization and diabetic macular edema. Ang-2 works as a vascular-destabilizing signal.
2. Vabysmo can typically be injected intravitreally once every 16 weeks.*

* Dosage and Administration for Age-related macular degeneration with subfoveal choroidal neovascularization in Japan: 6 mg (0.05 mL) of faricimab (genetical recombination) is administered by intravitreal injection once every 4 weeks typically for the first four times (loading period), but the number of injections can be reduced appropriately according to the patient's symptoms. In the subsequent maintenance period, it is typically administered by intravitreal injection once every 16 weeks. Dosage intervals are to be adjusted as appropriate according to the patient's symptoms, but the minimum interval is to be at least 8 weeks.
* Dosage and Administration for Diabetic macular edema in Japan: 6 mg (0.05 mL) of faricimab (genetical recombination) is administered by intravitreal injection once every 4 weeks typically for the first four times, but the number of injections can be reduced appropriately according to the patient's symptoms. Subsequently, it is typically administered by intravitreal injection once every 16 weeks after gradually extending the dosing interval. Dosage intervals are to be adjusted as appropriate according to the patient's symptoms, but the intervals are to be at least 4 weeks.

Source: Vabysmo general product information brochure

Indications

Indications

- **Age-related macular degeneration associated with subfoveal choroidal neovascularization**
- **Diabetic macular edema**

Precautions concerning indications

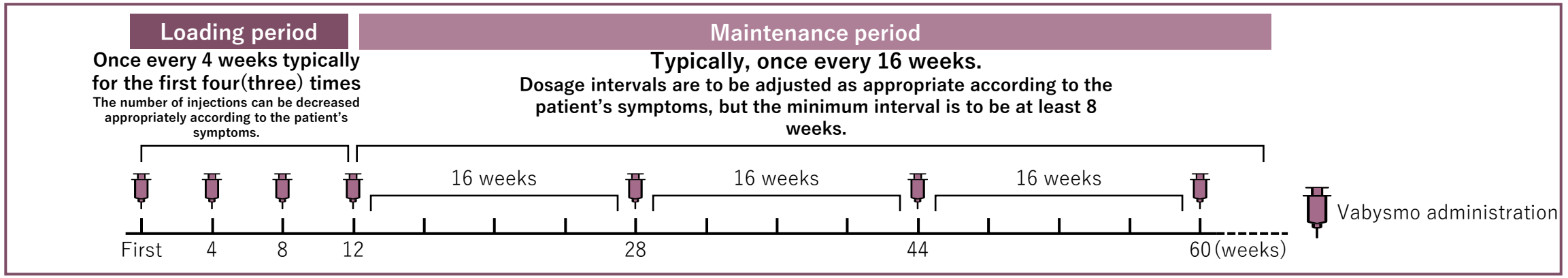
When starting treatment using Vabysmo, take into consideration the patient's prognosis, such as visual acuity, before deciding whether Vabysmo treatment is necessary.

Digitalized Package Insert of Vabysmo Solution for Intravitreal Injection 120 mg/mL (May 2022; Version 2)

Dosage and Administration (Age-Related Macular Degeneration with Subfoveal Choroidal Neovascularization)

Dosage and administration

6 mg (0.05 mL) of faricimab (genetical recombination) is administered by intravitreal injection once every 4 weeks typically for the first four times (loading period), but the number of injections can be reduced appropriately according to the patient's symptoms. In the subsequent maintenance period, it is typically administered by intravitreal injection once every 16 weeks. Dosage intervals are to be adjusted as appropriate according to the patient's symptoms, but the minimum interval is to be at least 8 weeks.



7. Precautions for Dosage and Administration (excerpt)

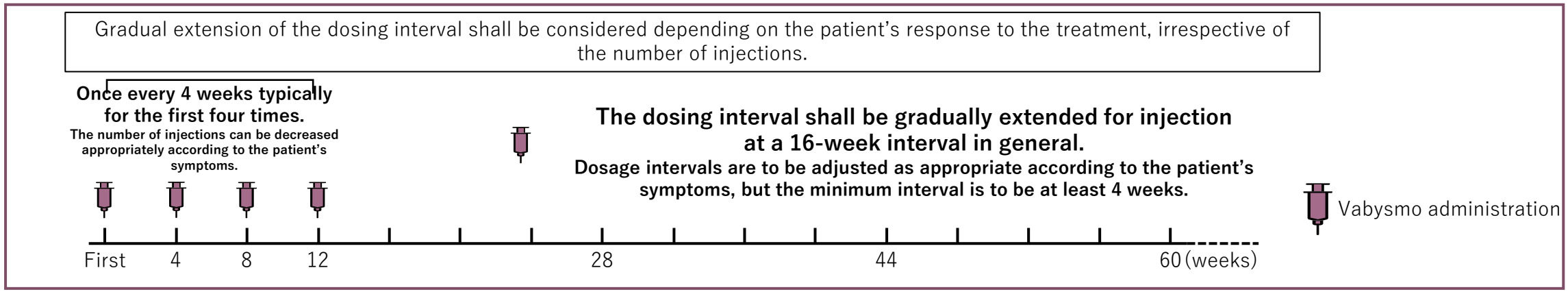
7.1 Binocular treatments are not conducted during clinical studies. When both eyes have lesions to be treated, carefully assess the benefits and risks associated with simultaneous treatment of both eyes before administering VABYSMO. Avoid administration of VABYSMO to both eyes on the same day during initial treatment; evaluate safety after administering VABYSMO to one eye before administering VABYSMO to the opposite eye.

7.2 Regarding the frequency of treatment during the loading period, consider the administration of intravitreal injection once every 4 weeks for the first three times according to the assessment of disease activity as appropriate. During the maintenance period, consider a dosing interval of e.g. 8 or 12 weeks if any findings of disease activity are observed.

Dosage and Administration (Diabetic Macular Edema)

Dosage and administration

6 mg (0.05 mL) of faricimab (genetical recombination) is administered by intravitreal injection once every 4 weeks typically for the first four times, but the number of injections can be reduced appropriately according to the patient's symptoms. Subsequently, it is typically administered by intravitreal injection once every 16 weeks after gradually extending the dosing interval. Dosage intervals are to be adjusted as appropriate according to the patient's symptoms, but the intervals are to be at least 4 weeks.



7. Precautions for Dosage and Administration (excerpt)

7.1 Binocular treatments are not conducted during clinical studies. When both eyes have lesions to be treated, carefully assess the benefits and risks associated with simultaneous treatment of both eyes before administering VABYSMO. Avoid administration of VABYSMO to both eyes on the same day during initial treatment; evaluate safety after administering VABYSMO to one eye before administering VABYSMO to the opposite eye.

7.3 After starting the treatment, consider extending the treatment interval gradually according to the treatment response, regardless of the number of injections. Then, monitor the disease activity on a regular basis and consider a dosing interval of e.g. 4, 8 and 12 weeks if any findings of disease activity are observed.

Digitalized Package Insert of Vabysmo Solution for Intravitreal Injection 120 mg/mL (March 2022; Version 1)

Adverse Reactions

Adverse Reactions

Since the following adverse reactions may occur, adequate observation shall be conducted to take an appropriate action such as discontinuation of the treatment for an abnormality, if applicable.

Clinically significant adverse reactions

Eye disorders

Intraocular inflammation (e.g., uveitis and vitritis; 1.0%), retinal pigment epithelial tear (0.4%), endophthalmitis (frequency unknown), and rhegmatogenous retinal detachment / retinal tear (frequency unknown) may develop. In a patient with history of intraocular inflammation related to the drug, and who has received readministration of Vabysmo, intraocular inflammation was reported to recur. [See Section 8.3.5]

Stroke

Ischemic stroke (0.05%), thrombotic cerebral infarction (0.05%), and lacunar stroke (0.05%) may develop. [See Sections 9.1.2 and 15.1.1]

Other adverse reactions

	Less than 1%	Frequency unknown
Eye disorders	Intraocular pressure increased, vitreous floaters, ocular hypertension, corneal abrasion, eye pain, and ocular discomfort	Conjunctival hemorrhage

Vabysmo Intravitreal Injection 120 mg/mL Risk Management Plan

Safety consideration

Significant identified risks

- Infectious endophthalmitis
- Intraocular inflammation
- Rhegmatogenous retinal detachment and retinal tears
- Retinal pigment epithelial tears（only nAMD）
- Intraocular pressure increased

Significant potential risks

- Arterial thromboembolic event

Important missing information

Not applicable

Drug safety monitoring plan

Normal activities

- Consideration (and implementation) of safety measures based on collection, confirmation, and analysis of adverse reactions, information from literature and academic societies, and reports of measures taken in foreign countries.

Additional activities

- post-marketing surveillance
- general use performance survey
- postmarketing clinical trial (nAMD,DME,PCV)

Risk minimization plan

Normal activities

- Preparation of approval information file
- Patient drug guide

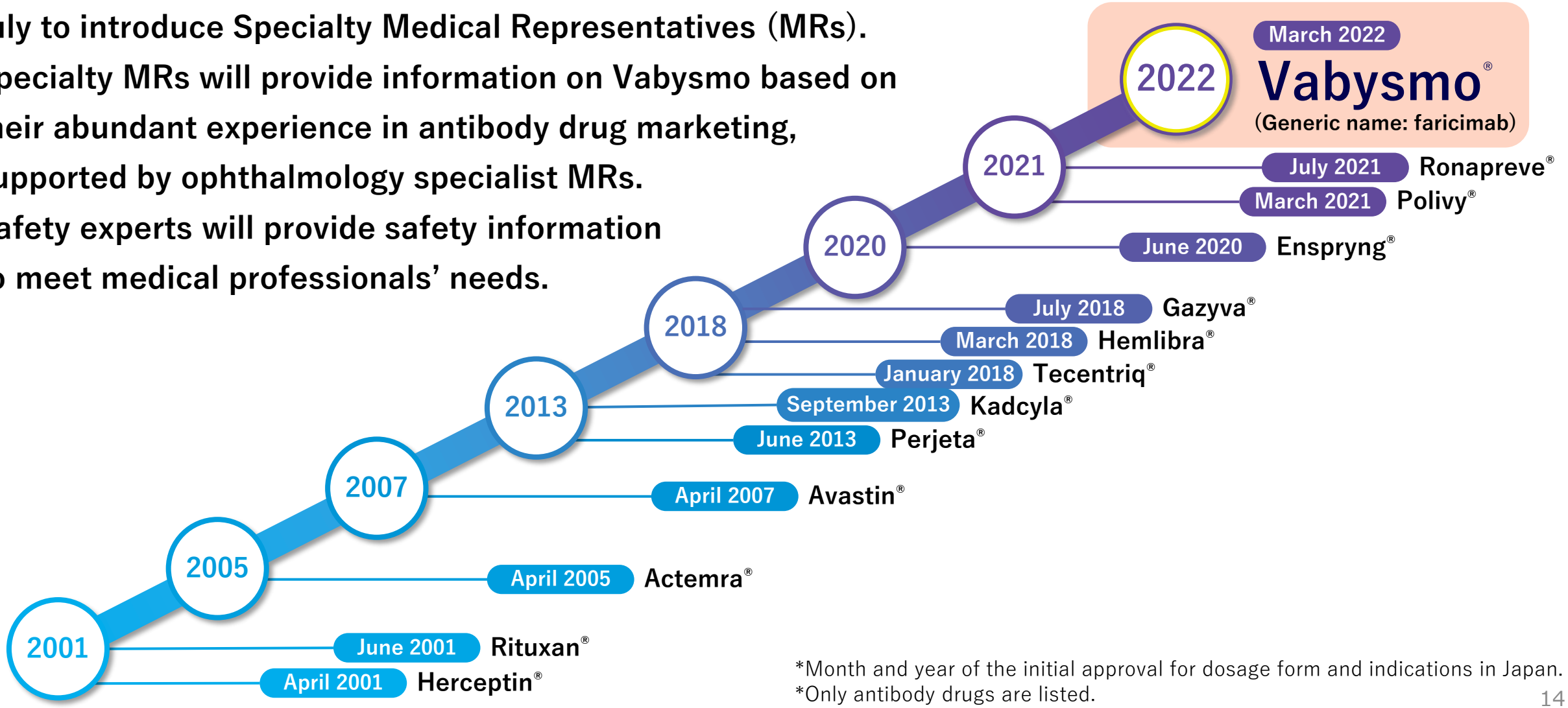
Additional activities

- Information provided by post-marketing surveillance
- Creation and distribution of materials for medical professionals (proper use guides)
- Creation and distribution of patient materials (patient handbooks)

The following abbreviations have been used in the preparation of this document.
DME: Diabetic macular edema, nAMD: Neovascular age-related macular degeneration, PCV: Polypoidal choroidal vasculopathy

Structure for Providing High-Value Services

- Marketing & Sales structure in Chugai will be reorganized in July to introduce Specialty Medical Representatives (MRs).
- Specialty MRs will provide information on Vabysmo based on their abundant experience in antibody drug marketing, supported by ophthalmology specialist MRs.
- Safety experts will provide safety information to meet medical professionals' needs.



*Month and year of the initial approval for dosage form and indications in Japan.
*Only antibody drugs are listed.

Information Website for Patients

Available now on the website Ever Visible.jp (Japanese only)
Further information, including eye frailty, for various patients and their families will be published on websites.

"Ever visible.jp (Japanese only) https://mieruwoitsumademo.jp

Extend your healthy eye span
Eye Frailty

Definition of Eye Frailty

A condition in which visual function is or is highly likely to be decreased by various external/internal factors that come with increased eye fragility with aging.

1)Strategic activities for "Eye Frailty" by the Japanese Journal of Ophthalmology https://www.nichigan.or.jp/member/journal/strategy/detail.html?itemid=393&dispmid=979 [Internet; Accessed May 2022]
2)Official website for awareness-raising activities of Eye Frailty by the Japanese Ophthalmologic Education Conference https://www.eye-frail.jp/[Internet; Accessed May 2022]

Summary of Vabysmo

1. The first bispecific antibody in ophthalmology, specifically binding to VEGF-A and Ang-2.

2. Vabysmo has been approved and launched in Japan for two indications of age-related macular degeneration associated with subfoveal choroidal neovascularization and diabetic macular edema simultaneously (the second country worldwide after the United States.)

3. Vabysmo is intravitreally injected once every four weeks typically for the first four times in the loading period. In the maintenance period, Vabysmo can be intravitreally injected typically once every 16 weeks.

4. Chugai aims to provide high-value services in ophthalmology for achieving better treatment outcomes with our abundant experience in antibody drug marketing.

VEGF-A: vascular endothelial growth factor-A, Ang-2: angiopoietin-2

Clinical Significance of Vabysmo®

Tomohiro Iida, M.D., Ph.D.,
Professor & Chairman, Department of Ophthalmology,
Tokyo Women's Medical University

Prepared in June 2022

Japanese Ophthalmological Society
COI Disclosure

Tomohiro Iida, M.D., Ph.D.,
Professor & Chairman, Department of Ophthalmology,
Tokyo Women's Medical University

【F】 Nidek, Topcon

【P】 Topcon

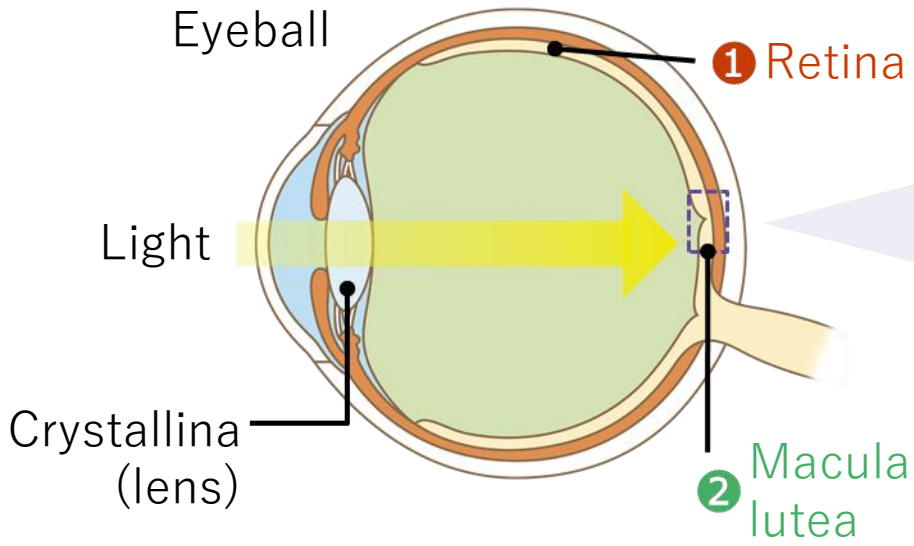
A disease-causing reduced vision with aging

Age-Related Macular Degeneration (AMD)

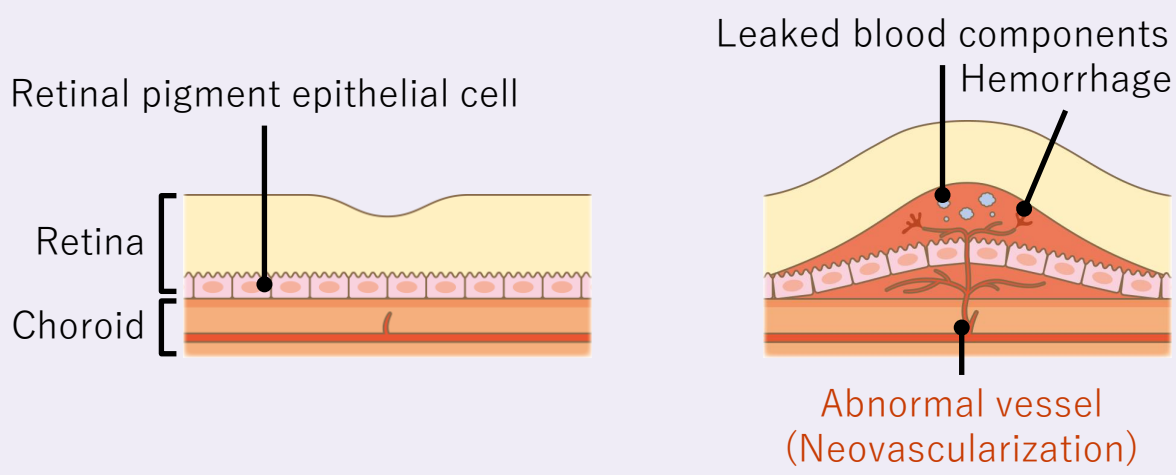
What Is Age-Related Macular Degeneration (AMD)?

- **An age-related disease with a disorder in the macula lutea that is important for visual acuity, leading to reduced vision.**

A cross-section of the eye



[conceptual illustration]



- There is a thin membrane called the “retina” behind the eye that recognizes visual information (❶). “Macula lutea” at the center of the retina is a particularly important region for recognizing the shape, color, and size of an object (❷).
- Age-related macular degeneration in which waste products remain in the macula lutea may damage the tissues and blood vessels through abnormal vascular extension, resulting in reduced vision or visual loss with disease progression.

Supervising editor: Professor Ayame Annabelle Okada, Department of Ophthalmology, Kyorin University School of Medicine

Types of AMD*

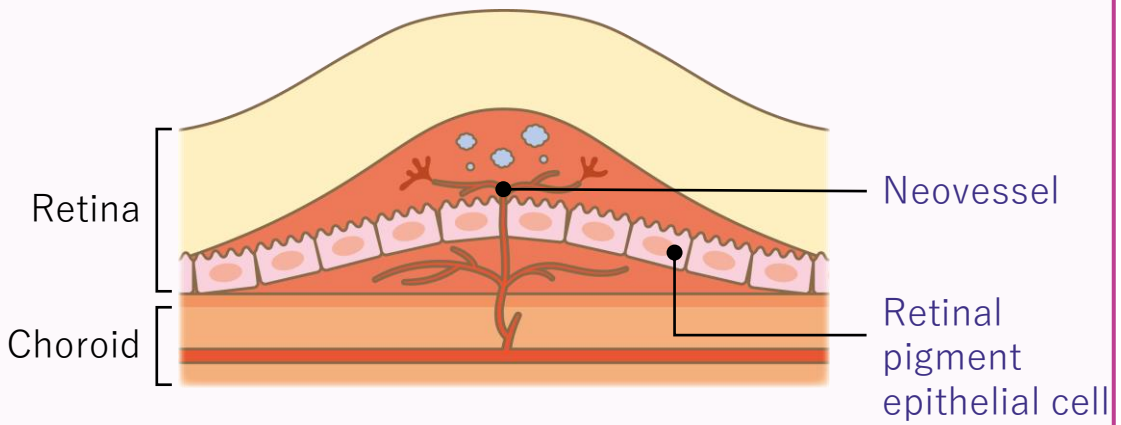
- **There are two types of conditions, exudative and atrophic AMD. In Japan, exudative AMD has been reported at a higher frequency.**

Exudative AMD

- Blood and blood components are leaked from generated neovessels.
- The macula lutea becomes dysfunctional due to the effects of blood and blood components leaked from generated neovessels, leading to reduced vision.

[conceptual illustration]

Exudative age-related macular degeneration

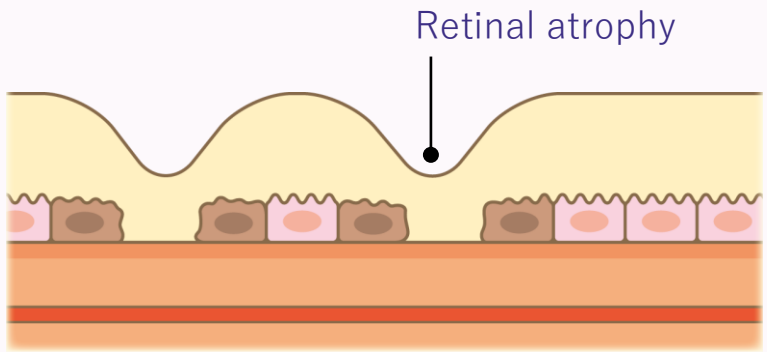


Atrophic AMD

- The macula lutea becomes dysfunctional due to cell shrinkage, leading to reduced vision without neovascularization.
- The disease progression is slow. There is no treatment available at present.

[conceptual illustration]

Atrophic age-related macular degeneration

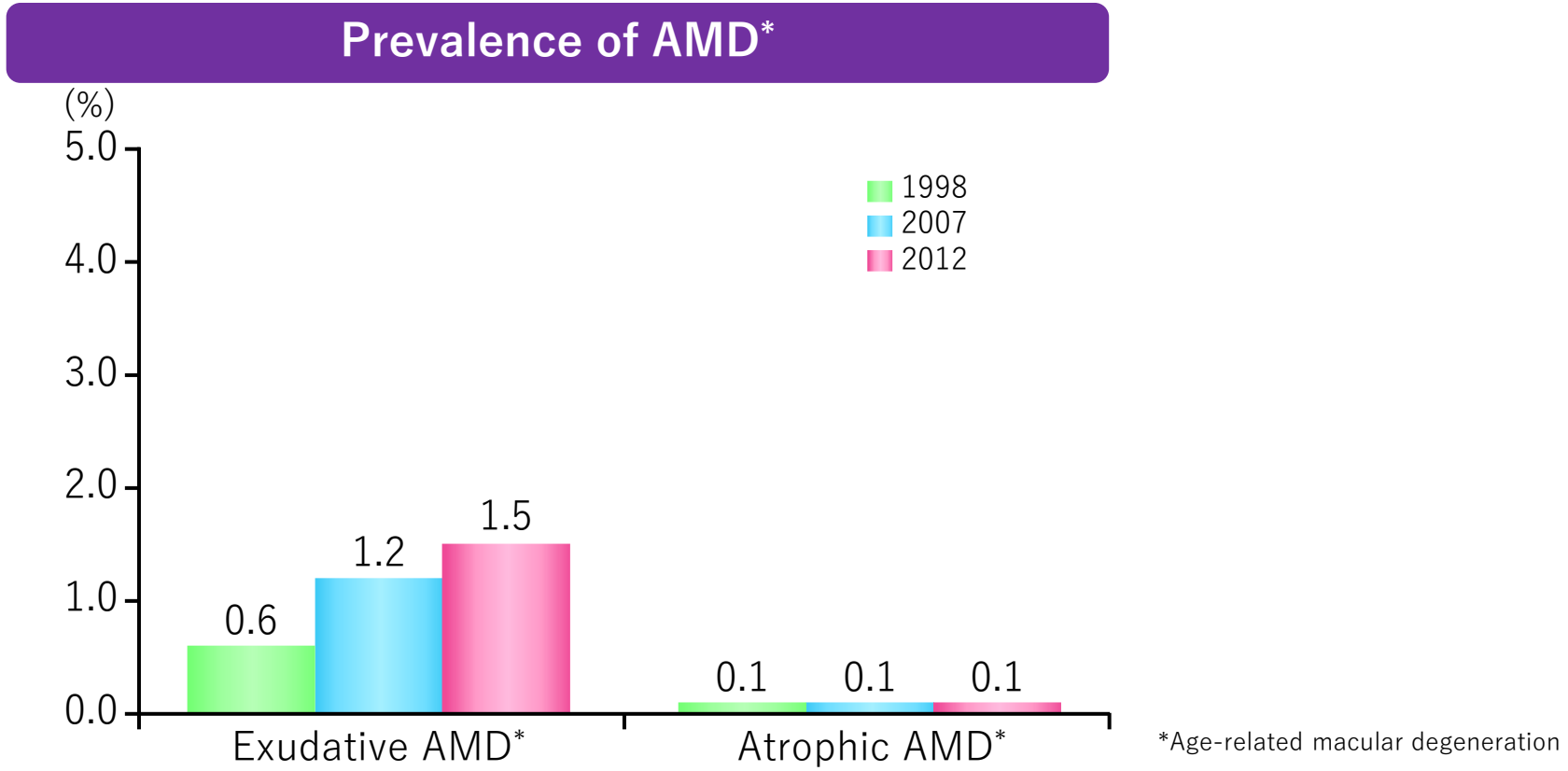


*Age-related macular degeneration

Supervising editor: Professor Ayame Annabelle Okada, Department of Ophthalmology, Kyorin University School of Medicine

Prevalence of AMD* in Japan

- Prevalence of exudative AMD* was 1.5% in 2012. When converted to the overall population aged 50 and older, the number of patients is estimated to be approximatively 0.9 million.



*Age-related macular degeneration

Subjects and methods: Follow-up was conducted in residents aged 50 and older, who underwent ophthalmic examinations in 1998, in Hisayama-machi, Kasuya-gun, Fukuoka, Japan (population: approximately 7,500). After diagnosis of age-related maculopathy by funduscopy, neovascular AMD (nAMD) or a condition with geographic atrophy was determined as late-stage age-related maculopathy, and a condition with drusen or abnormal retinal pigment epithelium (RPE) other than late-stage age-related maculopathy was determined as early age-related maculopathy.

1) Hashimoto S. et al. Journal of the Eye. 2019;36:135-9. 2) Miyazaki M, et al. Br J Ophthalmol. 2003;87:469-72. 3) Yasuda M, et al. Ophthalmology. 2009;116:2135-40.
4) e-Stat, demographic estimates / long-term data (H. 12 - 27) http://www.stat.go.jp/data/jinsui/index.htm (Accessed on March 23, 2022)

Symptoms of AMD*

- **AMD is characterized by difficulty seeing in a field where the patient is trying to see due to impairment of the macula lutea, the center of the retina, causing some symptoms such as metamorphopsia, reduced vision, central scotoma, and achromatopsia. [1)]**

Metamorphopsia	Central scotoma and reduced vision	Achromatopsia
Visual distortion	Visual loss in the middle part of vision, leading to reduced vision	Gradual decline in color perception

*Age-related macular degeneration

1) Information for the general public edited by the Japanese Journal of Ophthalmology Eye diseases: Age-related macular degeneration https://www.nichigan.or.jp/public/disease/name.html?pdid=52 (accessed on September 15, 2021)

Examinations and Diagnosis of Exudative AMD*

- **Retinal condition is examined by some procedures such as interview, visual acuity test, funduscopy, and optical coherence tomography.**

Funduscopy

- Color fundus photography: shall be conducted to obtain images of the macula lutea and the surrounding area.
- Fluorescein angiography: examines conditions with neovascularization and/or leakage of blood/blood components after injection of a contrast agent into the arm vessel.

Optical coherence tomography

- Optical coherence tomography (OCT): confirms macular conditions by obtaining cross-sectional images of the retina.
- Optical coherence tomography angiography (OCT Angiography): can noninvasively confirm vascular conditions in the retina and choroid without contrast agent.

Color fundus photograph of AMD*

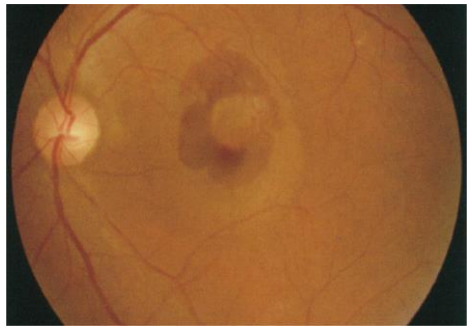
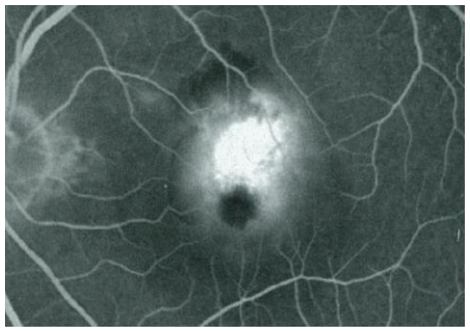
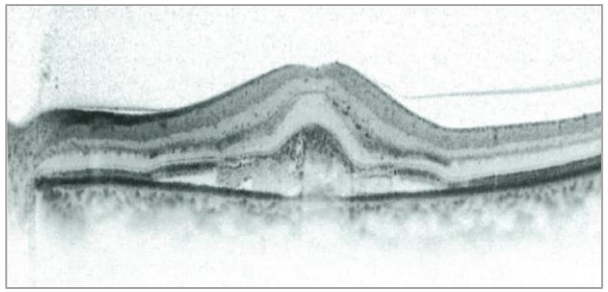


Image of AMD* by fluorescein angiography



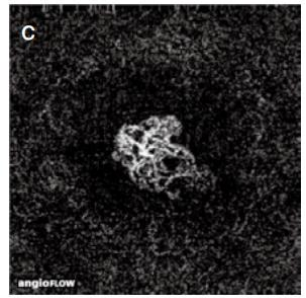
Yamamoto. A. Journal of the Eye. 2018;35 (extra edition):16-20.

A cross-sectional image of the retina with AMD* by OCT



Yamamoto. A. Journal of the Eye. 2018;35 (extra edition):16-20.

Picture A: neovessels in the choroid by OCT



Maruko. I. Journal of the Eye. 2017;34 (6):761-770.

*Age-related macular degeneration

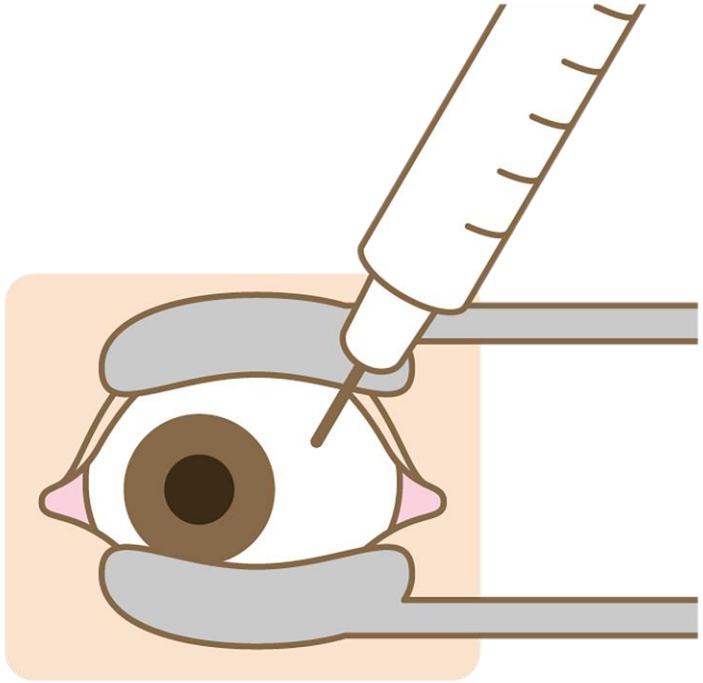
Supervising editor: Professor Ayame Annabelle Okada, Department of Ophthalmology, Kyorin University School of Medicine

Treatments of Exudative AMD*

- **Treatments of exudative AMD* include ocular drug injection, photodynamic therapy, and laser photocoagulation.**

Anti-VEGF intravitreal injection (anti-VEGF therapy):

- A therapy to suppress the growth of neovessels and edema related to leakage of blood components and inflammation by intraocular injection.
- Since the formed neovessels do not disappear typically, the treatment should be continued depending on the condition to maintain visual acuity.



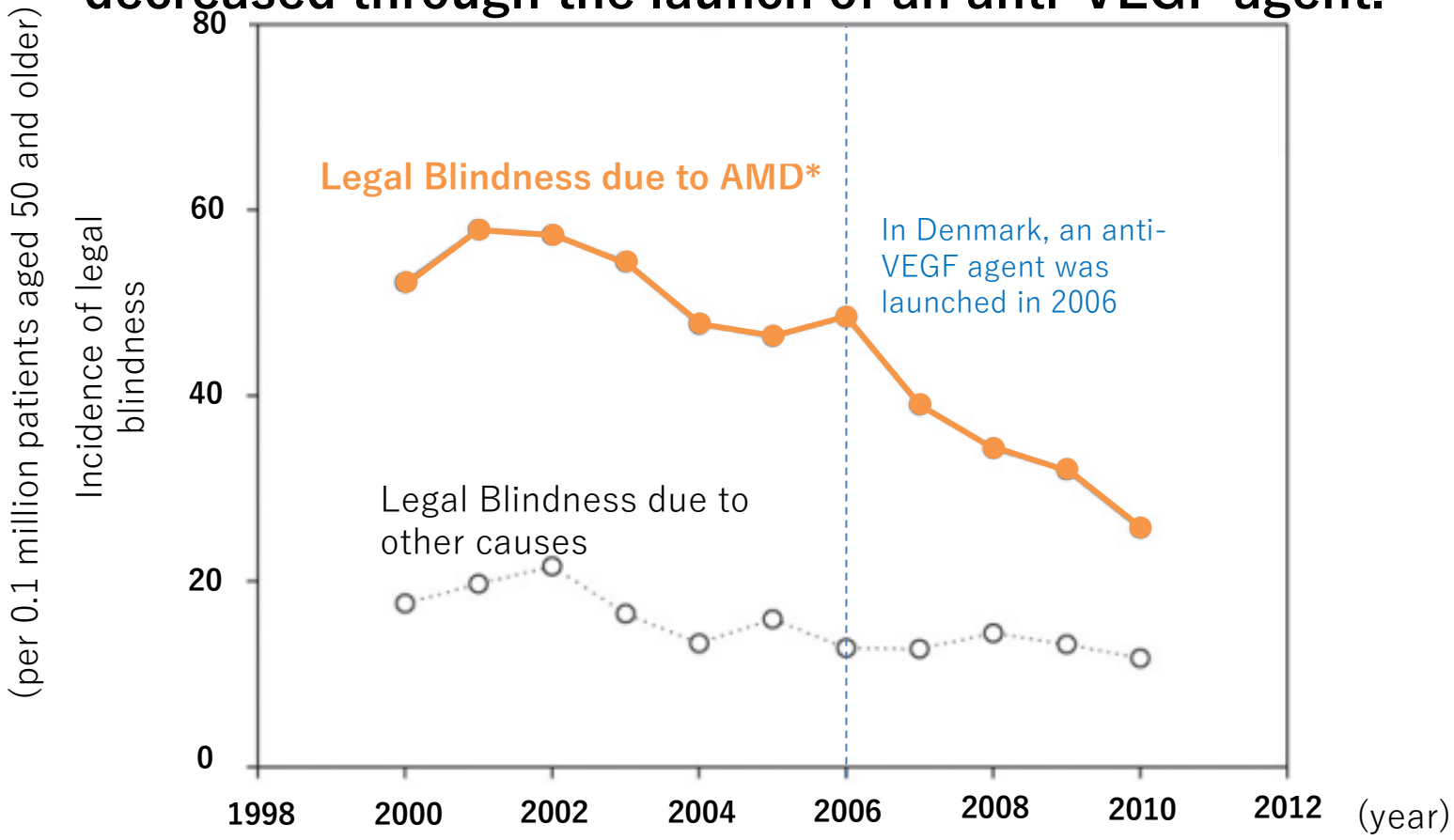
*Age-related macular degeneration

Supervising editor: Professor Ayame Annabelle Okada, Department of Ophthalmology, Kyorin University School of Medicine

Change in Legal Blindness due to AMD*

(Overseas data: Observational Study in Denmark)

Legal blindness due to AMD* has been markedly decreased through the launch of an anti-VEGF agent.



Subjects: A total of 11,848 patients with legal blindness aged 50 and older who were registered as members of the Danish Association of the Blind from 2000 to 2010 (8,827 patients were diagnosed with AMD).
Method: observational registration study. Incidence of legal blindness was examined by fiscal year, in visual loss due to AMD, and in visual loss due to a condition other than AMD among those subjects.

*Age-related macular degeneration

** Definition of social blindness in this study: Blind persons registered with the Danish Blindness Association for reasons such as best corrected visual acuity of 0.1 or less in both eyes

Bloch SB, et al. Am J Ophthalmol 2012; 153: 209-213

Assessment of Visual Acuity with ETDRS* Chart

Cases of treatment-naive patients and those showing post-treatment improvement in AMD**

- **AMD is one of the diseases that may reduce visual acuity, leading to visual loss without treatment. However, improvement in visual acuity became able to be expected thanks to the appearance of anti-VEGF therapy.**

Treatment-naive

Decimal visual acuity	ETDRS (letters)
0.2	50

-10 letters

Deteriorated

Baseline

Decimal visual acuity	ETDRS (letters)
0.32	60

+6 letters

Improved

After anti-VEGF therapy

Decimal visual acuity	ETDRS (letters)
0.42	66

Decimal visual acuity	ETDRS (letters)
0.010	
0.013	
0.016	
0.020	
0.025	5
0.032	10
0.040	15
0.050	20
0.063	25
0.079	30
0.10	35
0.13	40
0.16	45
0.20	50
0.25	55
0.32	60
0.40	65
0.50	70
0.63	75
0.80	80
1.00	85
1.26	90
1.59	95
2.00	100

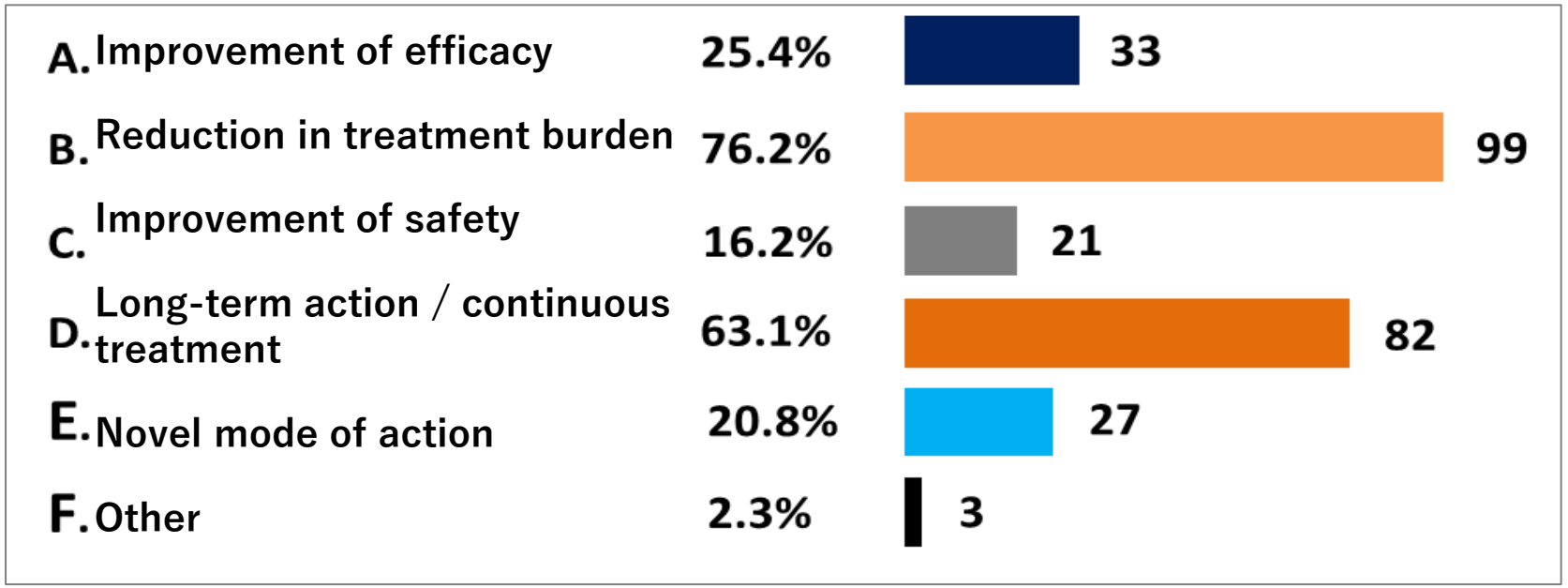
A 10-letter decrease in treatment-naive patients is based on data at 1 year in the treatment-naive group of MARINA study (Rosenfeld PJ, et al., 2006).
A 6-letter increase after anti-VEGF therapy is based on data at 1 year in the Vabysmo Q8W-Q16W groups of TENAYA and LUCERNE studies.

*Early Treatment Diabetic Retinopathy Study **Age-related macular degeneration

Unmet Medical Needs in Anti-VEGF Therapy Against Neovascular AMD*

- Unmet medical needs for retina specialists in anti-VEGF therapy against neovascular AMD* include a reduction in the treatment burden and long-term action of a treatment.

Unmet Medical Needs in Anti-VEGF Therapy Against neovascular AMD*



[Summary of surveillance] Responses to the Questionnaire for members of the Japanese Retina and Vitreous Society in 2020 (multiple choices allowed) No. of responders: 130

*Age-related macular degeneration

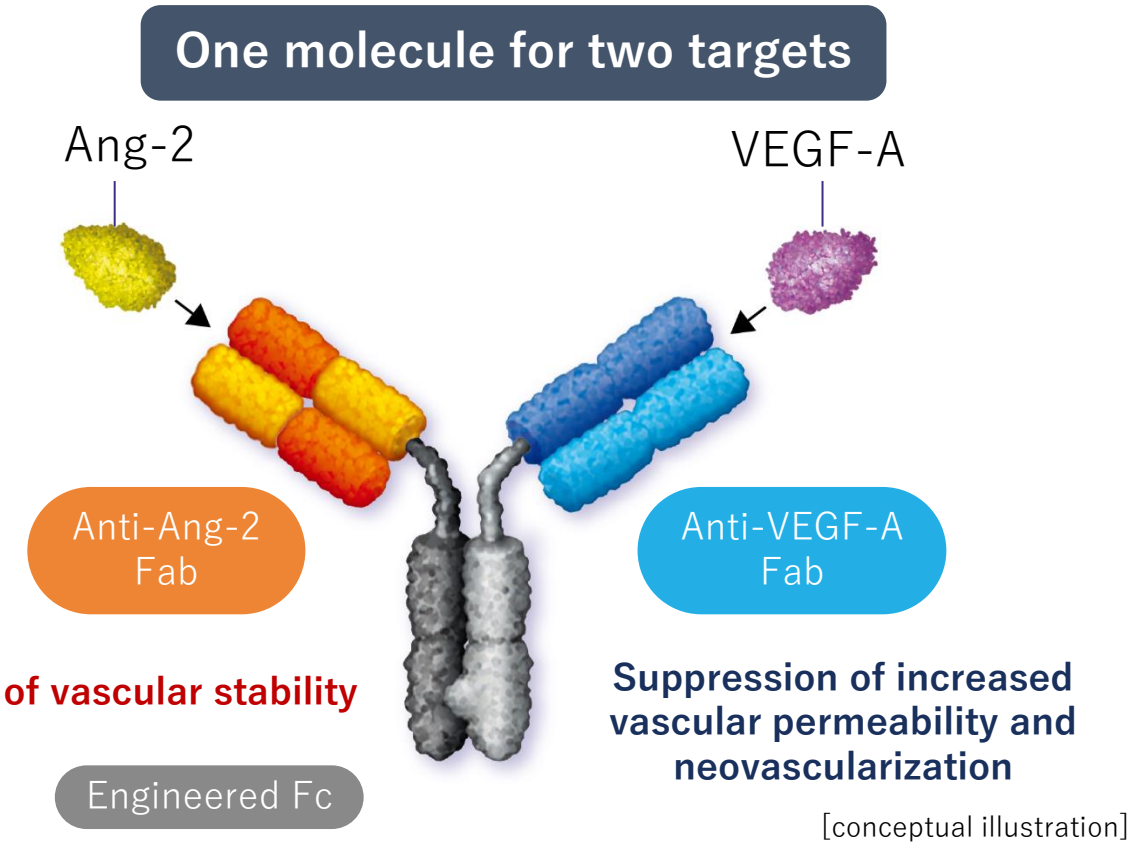
Preferences and Trends (PAT) Survey in Japan (Domestic data by the Japanese Retina and Vitreous Society)

Vabysmo

The first bispecific antibody specifically binding to VEGF-A and Ang-2 in ophthalmology

V A BYSMO

VEGF-A | Ang-2 | Bispecific | Molecule



[conceptual illustration]

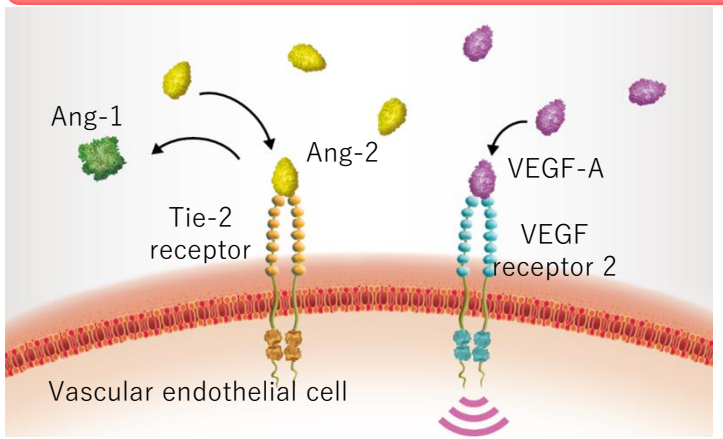
VEGF-A: vascular endothelial growth factor-A, Ang-2: angiopoietin-2

- Decrease in systemic exposure
- Reduction in proinflammatory effect

Mode of Action of Vabysmo

- **Vabysmo inhibits both VEGF-A and Ang-2 by one molecule. Expected inhibitory effects of Vabysmo against Ang-2 mainly include suppression of vascular destabilization by pericyte deficit, increased vascular permeability, and increased sensitivity to VEGF-A. The expected inhibitory effects against VEGF-A mainly include suppression of increased vascular permeability, neovascularization, and inflammation.**

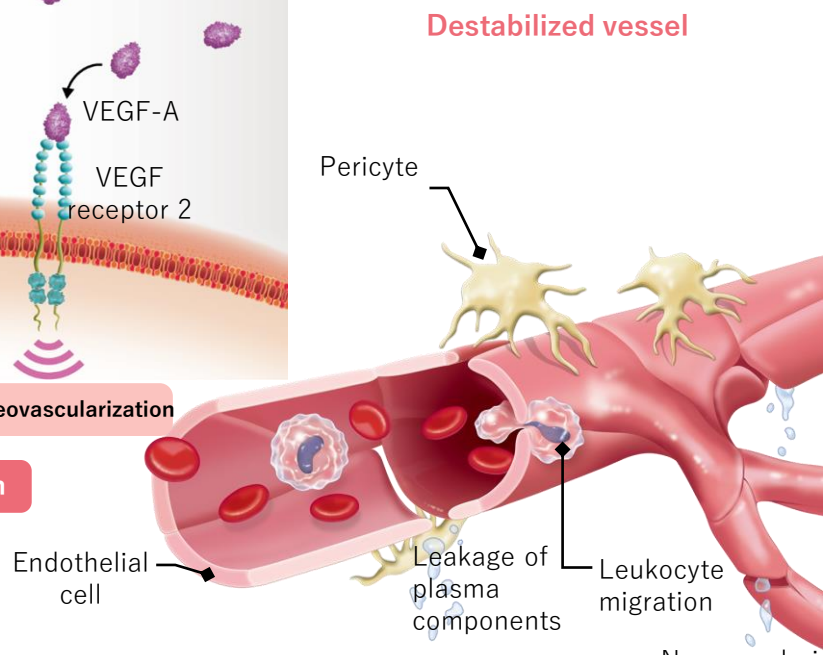
Coordination between VEGF-A and Ang-2



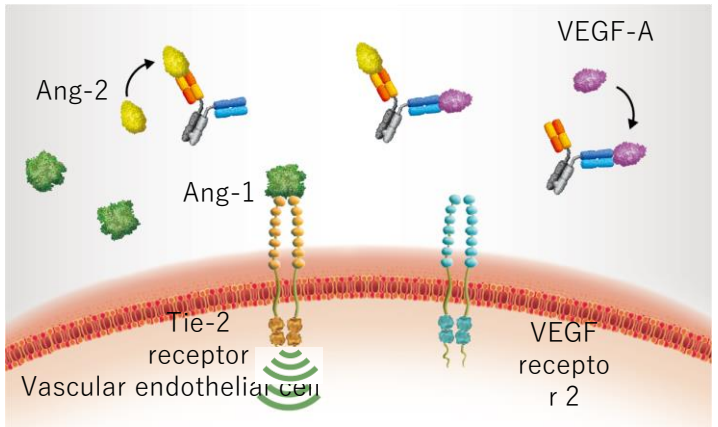
Inflammation | **Increased permeability** | **Neovascularization**

Vascular destabilization

(conceptual illustration)



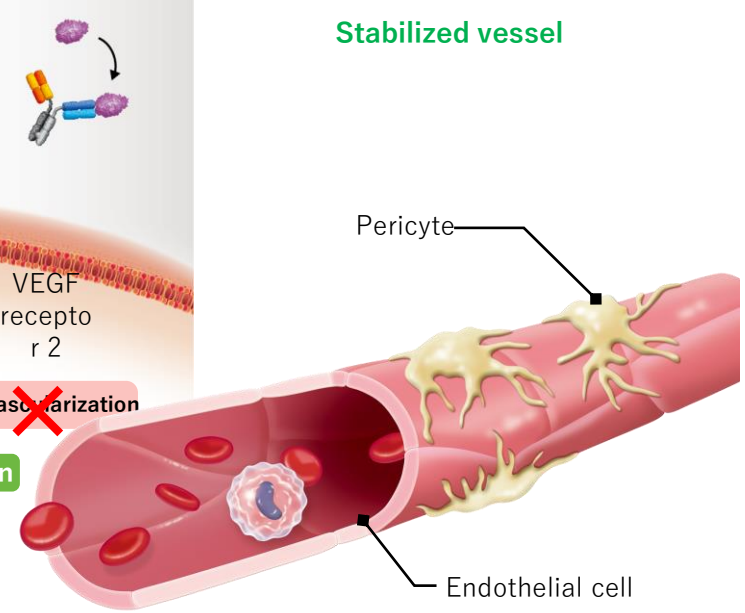
Action of Vabysmo



Inflammation ✕ | **Increased permeability** ✕ | **Neovascularization** ✕

Suppression of vascular destabilization

(conceptual illustration)

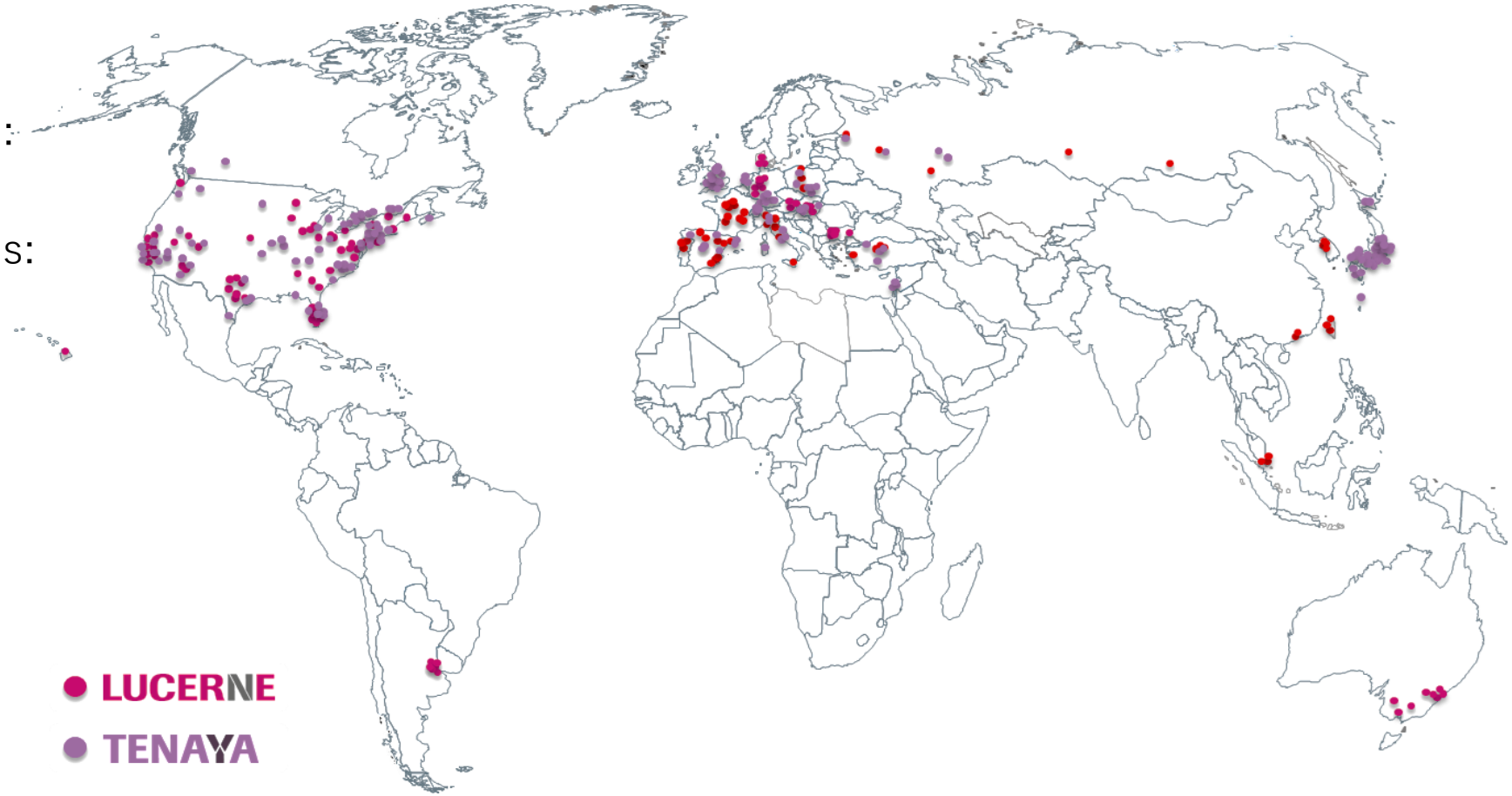


VEGF-A: vascular endothelial growth factor-A, Ang-2: angiopoietin-2, Ang-1: angiopoietin-1

1) Ichinose, A. (Ed.). Thrombosis, Hemostasis, and Vascular Sciences. 2005, P36-37. CHUGAI-IGAKUSHA.; 2) Lee J, et al. Invest Ophthalmol Vis Sci. 2014;55(4):2191–9.; 3) Regula JT, et al. EMBO Mol Med. 2016;8(11):1265-88. with correction in Regula JT, et al. EMBO Mol Med. 2019;11(5):e10666. (conflict of interest: Employees of Roche Ltd. [at the time of experiment], Roche Diagnostics GmbH, and F. Hoffmann-La Roche Ltd. are included in the authors) 4)Hammes HP, et al. Diebetes. 2004;53(4):1104-10. 5) Aiello LP, et al. N Engl J Med. 1994; 331(22):1480-7. 6)Benest AV, et al. PLoS One. 2013;8(8):e70459. 7)Oshima Y, et al. J Cell Physiol. 2004;199(3):412-7. 8)Peters S, et al. Cytokine. 2007;40(2):144-50. 9)Oh H, et al. J Biol Chem. 1999;274:15732-9. 10)Rangasamy S, et al. Invest Ophthalmol Vis Sci. 2011;52:3784-91.

Clinical Studies of Vabysmo in Neovascular AMD* (TENAYA and LUCERNE Studies)

- No. of enrolled patients: **1,329**
- No. of participating sites: **271**



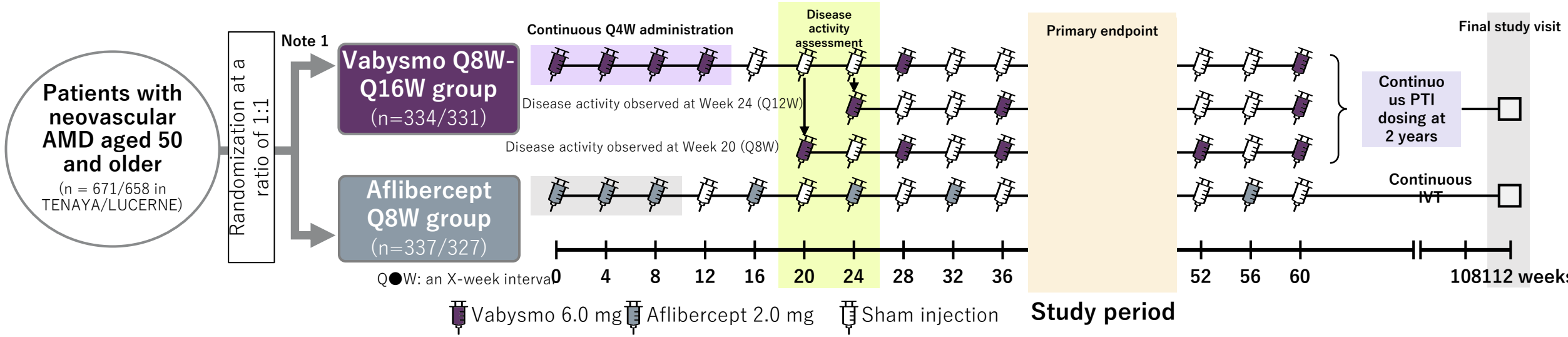
*Age-related macular degeneration

1) Evaluation material for approval: Global phase III study (GR40306 [TENAYA] study); 2) Evaluation material for approval: Overseas phase III clinical study (GR40844 [LUCERNE] study); 3)Heier JS, et al. Lancet. 2022;399(10326):729-40

Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

Study Overview: Design/Dosing Regimen

Study design	Multicenter, randomized, active control, double-blind, parallel, comparative study
Subjects	Patients with neovascular AMD* aged 50 and older: 671 patients (52 in Japanese subgroup) in TENAYA and 658 in LUCERNE.
Dosing regimen	• Subjects shall be randomly assigned to a group administered Vabysmo at up to a 16-week interval (Q8W-Q16W) or another group administered aflibercept at an 8-week interval (Q8W) at a ratio of 1:1. • In the Vabysmo Q8W-Q16W group, Vabysmo 6.0 mg shall be administered four times at a 4-week interval, and the fixed dose shall be continued until Week 60 at an interval of 8, 12, or 16 weeks based on disease activity assessments at Weeks 20 and 24, followed by administration of PTI** regimen until Week 108. • In the aflibercept Q8W group, aflibercept 2.0 mg shall be administered three times at a 4-week interval and then continued at an 8-week interval until Week 108.



*Age-related macular degeneration ** personalized treatment interval

1) Evaluation material for approval: Global phase III study (GR40306 [TENAYA] study); 2) Evaluation material for approval: Overseas phase III clinical study (GR40844 [LUCERNE] study);
3)Heier JS, et al. Lancet. 2022;399(10326):729-40.

Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

Study Overview: Endpoints

End point	Efficacy	Primary endpoint (confirmatory endpoint)	**Mean values of changes in mean BCVA score from baseline at Weeks 40, 44, and 48 (shall be measured with ETDRS visual acuity chart)**
		Key secondary endpoint	• **Mean changes in BCVA scores from baseline** • **Ratios of patients by dosing interval at Week 48 in the Vabysmo Q8W-Q16W group** • Ratios of patients who achieved improvement of at least 15 letters from baseline BCVA score at Weeks 40, 44, and 48 (mean) • Ratios of patients who avoided deterioration of at least 15 letters from baseline BCVA score at Weeks 40, 44, and 48 (mean) • **Mean changes in CST scores from baseline at Weeks 40, 44, and 48 and the time-course in the mean changes** • Ratio of patients without intraretinal fluid • Ratio of patients without subretinal fluid
		Exploratory endpoint	Mean changes and time-dependent changes in NEI VFQ-25 score from baseline [reference data]
	Key safety endpoint		• **Incidence and severity of ocular adverse events** • **Incidence and severity of non-ocular adverse events**

BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; NEI VFQ-25, National Eye Institute Visual Function Questionnaire-25

1) Evaluation material for approval: Global phase III study (GR40306 [TENAYA] study); 2) Evaluation material for approval: Overseas phase III clinical study (GR40844 [LUCERNE] study);
3)Heier JS, et al. Lancet. 2022;399(10326):729-40.

Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

Patient Characteristics

		TENAYA study				LUCERNE study	
		ITT population		Japanese subpopulation		ITT population	
		Vabysmo Q8W-Q16W group (n=334)	Aflibercept Q8W group (n=337)	Vabysmo Q8W-Q16W group (n=26)	Aflibercept Q8W group (n=26)	Vabysmo Q8W-Q16W group (n=331)	Aflibercept Q8W group (n=327)
Years of age, mean (SD)		75.9(8.6)	76.7(8.8)	71.9(8.0)	70.3(9.8)	74.8(8.4)	76.1(8.6)
Sex (n [%])	Female	191(57.2)	211(62.6)	4(15.4)	9(34.6)	203(61.3)	188(57.5)
BCVA score (No. of letters), mean (SD)		61.3(12.5)	61.5(12.9)	58.8(15.1)	59.4(13.4)	58.7(14.0)	58.9(13.3)
Category of BCVA score (No. of letters), n (%)	≥ 74 (Equivalent to 20/32 or higher#)	47(14.1)	52(15.4)	2(7.7)	3(11.5)	45(13.6)	39(11.9)
	73 to 55 (Equivalent to 20/40 to 20/80#)	200(59.9)	201(59.6)	15(57.7)	15(57.7)	181(54.7)	183(56.0)
	≤ 54 (Equivalent to 20/80 or lower#)	87(26.0)	84(24.9)	9(34.6)	8(30.8)	105(31.7)	105(32.1)
CST (ILM-RPE; μm), mean (SD) [a,b]		360.5(124.1)	356.1(107.0)	365.2(172.9)	340.3(121.5)	353.1(120.1)	359.0(131.1)

Q●W, an X-week interval; ITT, Intention-to-treat; BCVA, best corrected visual acuity; CST, central subfield thickness; IRF, intraretinal fluid; SD, standard deviation; SRF, subretinal fluid

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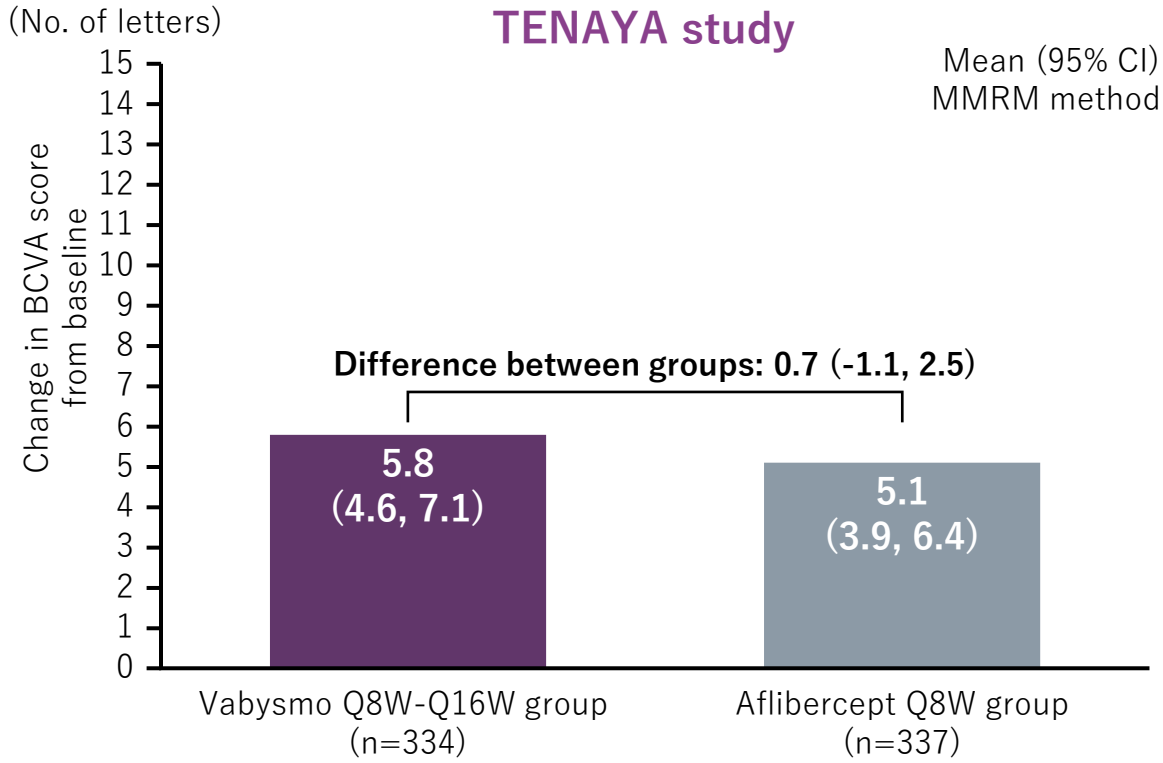
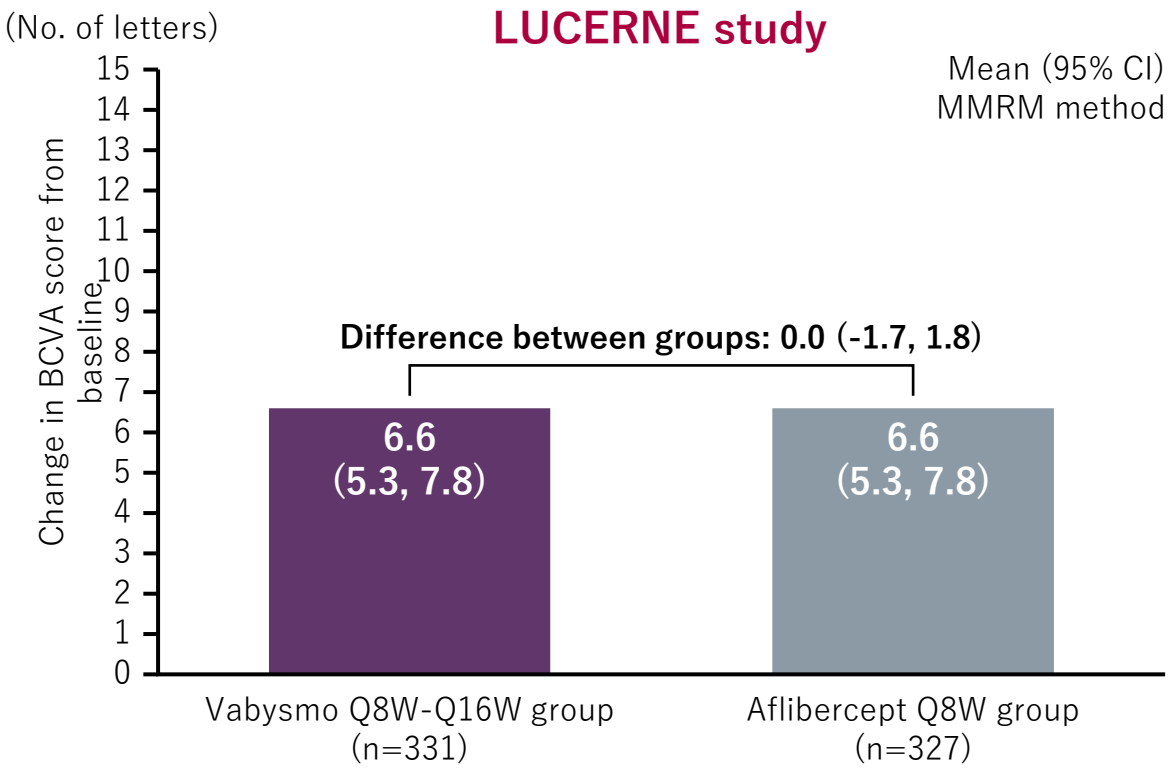
3)Heier JS, et al. Lancet. 2022;399(10326):729-40.

Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

Primary Endpoint: Mean Change from Baseline in Mean BCVA Score at 40/44/48 Weeks

- **Non-inferiority of the Vabysmo Q8W-Q16W group to the aflibercept Q8W group was examined in both studies.**





BCVA: best corrected visual acuity

Q●W: an X-week interval

MMRM: Mixed effect Models for Repeated Measures

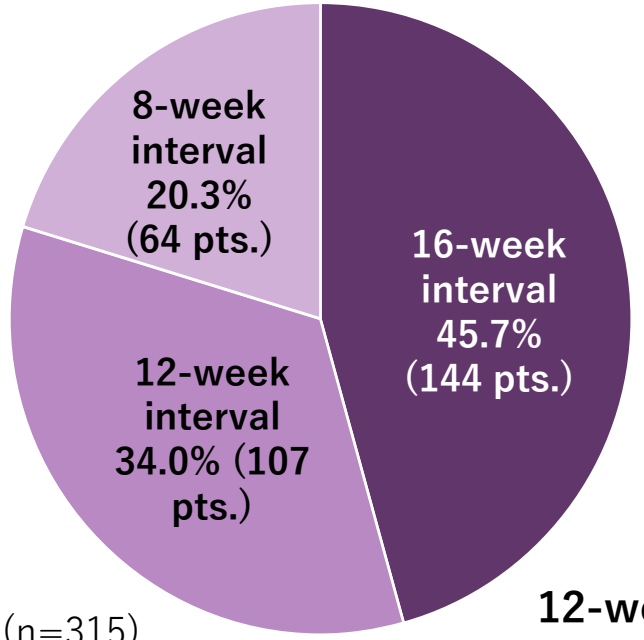
1) Evaluation material for approval: Global phase III study (GR40306 [TENAYA] study); 2) Evaluation material for approval: Overseas phase III clinical study (GR40844 [LUCERNE] study);
3)Heier JS, et al. Lancet. 2022;399(10326):729-40.

Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

Secondary Endpoint: Percentage of Patients by Dosing Interval of Vabysmo at Week 48

- Over 40% and 70% of patients achieved the 16-week and 12-week dosing intervals, respectively.

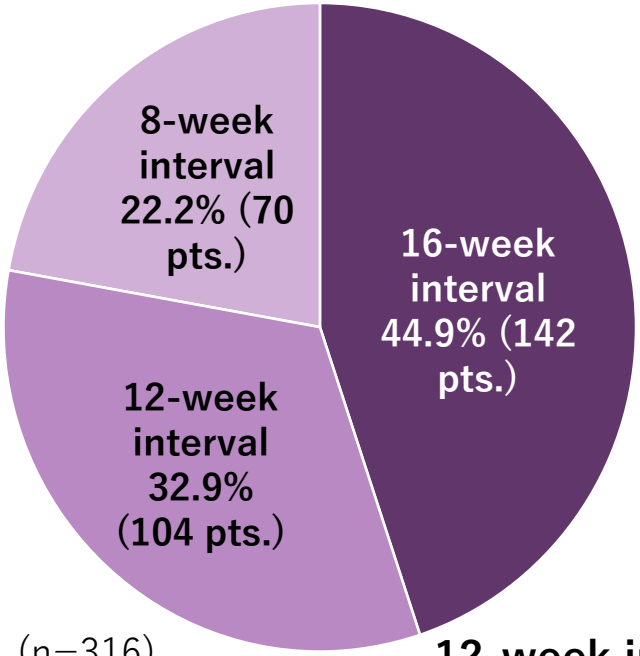
TENAYA study



(n=315)

12-week interval + 16-week interval 79.7%

LUCERNE study



(n=316)

12-week interval + 16-week interval 77.8%

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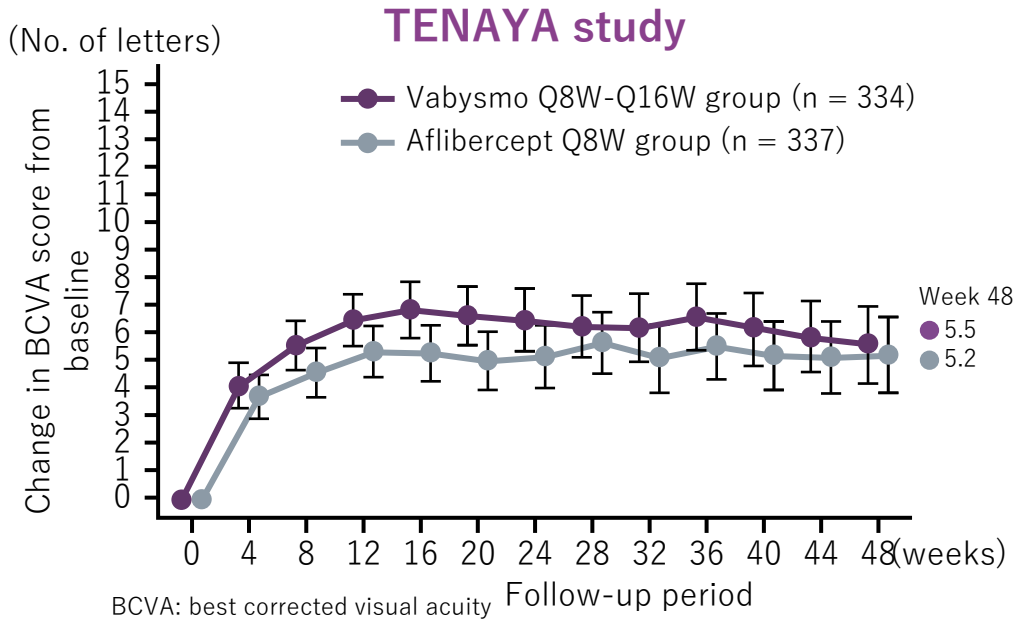
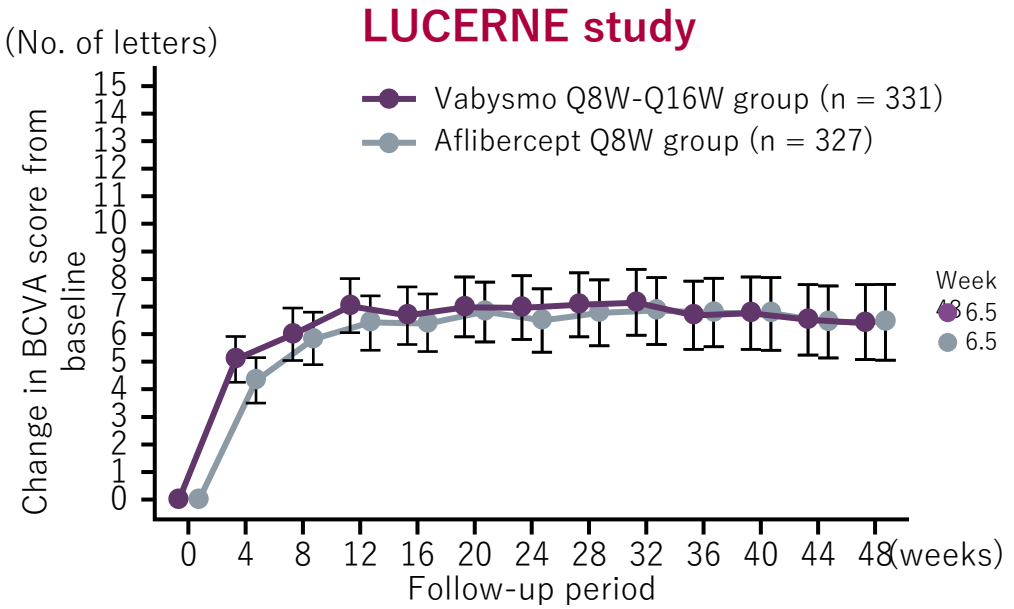
Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

Secondary Endpoint: Average change from Baseline in BCVA Score

- The average change from baseline in BCVA scores was as follows.





BCVA: best corrected visual acuity
Q●W: an X-week interval

Dosing regimen

Follow-up period (week)	0	4	8	12	16	20	24	28	32	36	40	44	48
Vabysmo Q8W-Q16W group	●	●	●	●	●	●	●	●	●	●	●	●	●
						↓	↓	●	●	●	●	●	●
						●	●	●	●	●	●	●	●
Aflibercept Q8W group	●	●	●	●	●	●	●	●	●	●	●	●	●

Disease activity assessment
Week 20 with disease activity (DA), Q8W; Week 24 with DA, Q12W; and Weeks 20/24 with DA, Q16W.

Primary endpoint

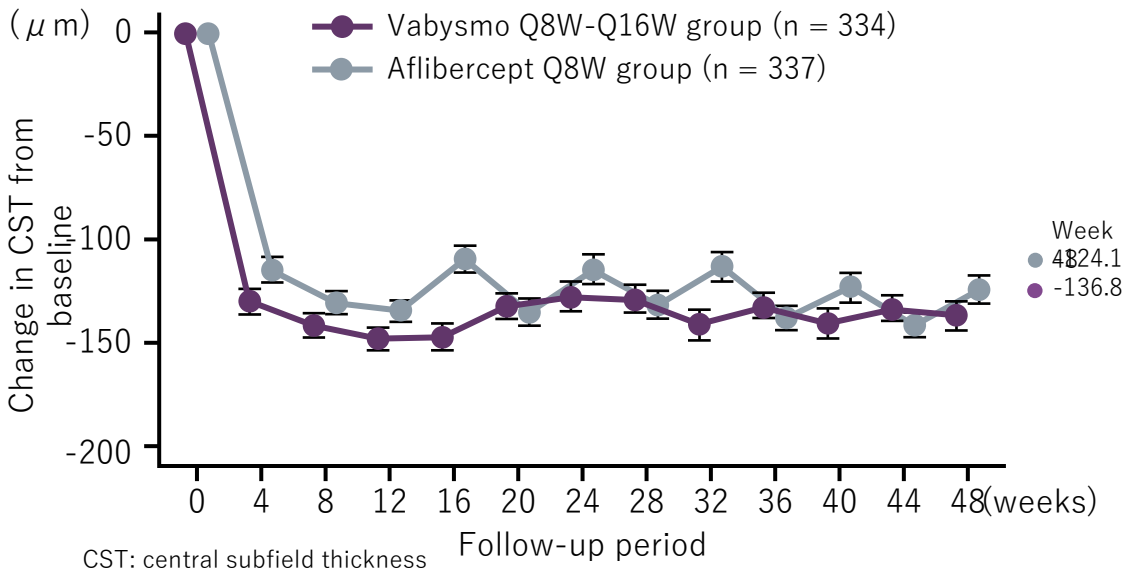
● Vabysmo 6.0 mg
● Aflibercept 2.0 mg
Sham injection

1) Evaluation material for approval: Global phase III study (GR40306 [TENAYA] study); 2) Evaluation material for approval: Overseas phase III clinical study (GR40844 [LUCERNE] study);
3)Heier JS, et al. Lancet. 2022;399(10326):729-40.

Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

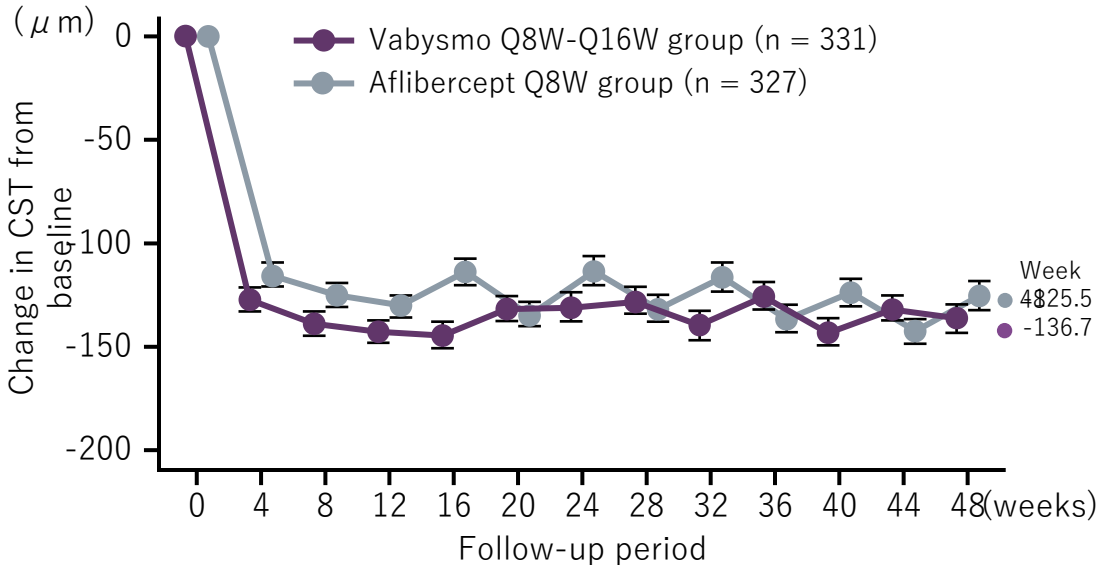
Secondary endpoint: Mean Change from Baseline and Mean Change in Central Retinal Thickness at 40/44/48 Weeks

TENAYA study



CST: central subfield thickness

LUCERNE study



Dosing regimen

Follow-up period (week)	0	4	8	12	16	20	24	28	32	36	40	44	48
Vabysmo Q8W-Q16W group	●	●	●	●	●	●	●	●	●	●	●	●	●
						↓	↓						
						●	●	●	●	●	●	●	●
Aflibercept Q8W group	●	●	●	●	●	●	●	●	●	●	●	●	●

Vabysmo 6.0 mg
Aflibercept 2.0 mg
Sham injection

Disease activity assessment
Week 20 with disease activity (DA), Q8W; Week 24 with DA, Q12W; and Weeks 20/24 with DA, Q16W.

Primary endpoint

1) Evaluation material for approval: Global phase III study (GR40306 [TENAYA] study); 2) Evaluation material for approval: Overseas phase III clinical study (GR40844 [LUCERNE] study);
3)Heier JS, et al. Lancet. 2022;399(10326):729-40.

Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

Safety 1: Adverse Reactions in the Study Eyes

Item name MedDRA preferred term	TENAYA study				LUCERNE study	
	Overall population		Japanese subgroup in the ITT population		Overall population	
	Vabysmo Q8W-Q16W group (n=373)	Aflibercept Q8W group (n=377)	Vabysmo Q8W-Q16W group (n=66)	Aflibercept Q8W group (n=67)	Vabysmo Q8W-Q16W group (n=331)	Aflibercept Q8W group (n=326)
All adverse reactions developed in the study eyes	**10 (2.7)**	**10 (2.7)**	**2 (3.0)**	**2 (3.0)**	**10 (3.0)**	**9 (2.8)**
The total No. of adverse reactions developed in the study eyes	**12**	**10**	**2**	**2**	**12**	**10**
Retinal pigment epithelial tear	5 (1.3)	1 (0.3)	0	0	3 (0.9)	1 (0.3)
Uveitis	2 (0.5)	1 (0.3)	1 (1.5)	0	2 (0.6)	1 (0.3)
Intraocular pressure increased	0	3 (0.8)	0	1 (1.5)	1 (0.3)	1 (0.3)
Vitritis	1 (0.3)	0	0	0	2 (0.6)	1 (0.3)
Iridocyclitis	0	0	0	0	2 (0.6)	1 (0.3)
Iritis	2 (0.5)	0	1 (1.5)	0	0	1 (0.3)
Ocular hypertension	0	2 (0.5)	0	0	1 (0.3)	0
Vitreous floaters	0	0	0	0	1 (0.3)	1 (0.3)
Cataract subcapsular	0	1 (0.3)	0	1 (1.5)	0	0
Dry age-related macular degeneration	0	1 (0.3)	0	0	0	0
Asteroid hyalosis	1 (0.3)	0	0	0	0	0
Keratic precipitates	0	1 (0.3)	0	0	0	0
Non-infectious endophthalmitis	0	0	0	0	0	1 (0.3)
Post procedural inflammation	0	0	0	0	0	1 (0.3)

Unless otherwise specified, the values refer to n (%). Drug-related adverse events in MedDRA Version 24.0 were considered as adverse reactions. The ratios (%) were calculated in the safety analysis set. For totalizing the frequencies of preferred terms, when an adverse event developed multiple times in a patient, the event was counted only once. For totalizing the numbers of adverse reactions, when an adverse event developed multiple times in a patient, all of the events were counted. Adverse events observed until Day 377 (the last day within a period until Week 52) are included.

Q●W: an X-week interval

1) Evaluation material for approval: Global phase III study (GR40306 [TENAYA] study); 2) Evaluation material for approval: Overseas phase III clinical study (GR40844 [LUCERNE] study);
3)Heier JS, et al. Lancet. 2022;399(10326):729-40.

Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

Safety 2: Non-Ocular Adverse Reactions

Item name MedDRA preferred term	TENAYA study				LUCERNE study	
	Overall population		Japanese subgroup in the ITT population		Overall population	
	Vabysmo Q8W-Q16W group (n=373)	Aflibercept Q8W group (n=377)	Vabysmo Q8W-Q16W group (n=66)	Aflibercept Q8W group (n=67)	Vabysmo Q8W-Q16W group (n=331)	Aflibercept Q8W group (n=326)
All non-ocular adverse reactions	**1 (0.3)**	**2 (0.5)**	**1 (1.5)**	**1(1.5)**	**2 (0.6)**	**0 (0.0)**
The total No. of adverse reactions developed in the study eyes	**1**	**2**	**1**	**1**	**2**	**0**
Nervous system disorders	**0**	**1 (0.3)**	**0**	**0**	**1 (0.3)**	**0**
Cerebrovascular accident	0	1 (0.3)	0	0	0	0
Thrombotic cerebral infarction	0	0	0	0	1 (0.3)	0
Cardiac disorders	**0**	**0**	**0**	**0**	**1 (0.3)**	**0**
Cardiac failure	0	0	0	0	1 (0.3)	0
Gastrointestinal disorder	**1 (0.3)**	**0**	**1 (1.5)**	**0**	**0**	**0**
Ischemic enteritis	1 (0.3)	0	1 (1.5)	0	0	0
Vascular disorders	**0**	**1 (0.3)**	0	**1 (1.5)**	**0**	**0**
Hypertension	0	1 (0.3)	0	1 (1.5)	0	0

totalizing the frequencies of preferred terms, when an adverse event developed multiple times in a patient, the event was counted only once. For totalizing the numbers of adverse reactions, when an adverse event developed multiple times in a patient, all of the events were counted. Adverse events observed until Day 377 (the last day within a period until Week 52) are included.
Q●W: an X-week interval

1) Evaluation material for approval: Global phase III study (GR40306 [TENAYA] study); 2) Evaluation material for approval: Overseas phase III clinical study (GR40844 [LUCERNE] study);
3)Heier JS, et al. Lancet. 2022;399(10326):729-40.

Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

Adverse Reactions Related to Intraocular Inflammation

- **In combined analyses for both studies, adverse reactions related to intraocular inflammation were observed in 10 subjects of groups treated with Vabysmo at 8- to 16-week intervals (Q8W-Q16W) and 8 of a group treated with aflibercept at an 8-week interval (Q8W).**

		TENAYA study		LUCERNE study		Overall nAMD	
		Vabysmo Q8W-Q16W group (n=373)	Aflibercept Q8W group (n=377)	Vabysmo Q8W-Q16W group (n=331)	Aflibercept Q8W group (n=326)	Vabysmo Q8W-Q16W group (n=704)	Aflibercept Q8W group (n=703)
Adverse Reactions		5 (1.3)	2 (0.5)	5(1.5)	6 (1.8)	10 (1.4)	8 (1.1)
Serious adverse reaction other than death		1 (0.3)	0	3 (0.9)	2 (0.6)	4 (0.6)	2 (0.3)
Severity	Mild	4 (1.1)	1 (0.3)	2 (0.6)	3 (0.9)	6 (0.9)	3 (0.4)
	Moderate	1 (0.3)	2 (0.5)	3 (0.9)	3 (0.9)	4 (0.6)	5 (0.7)
	Severe	1 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.1)
Adverse reaction leading to discontinuation of treatment		1 (0.3)	0	4 (1.2)	2 (0.6)	5 (0.7)	2 (0.3)

Unless otherwise specified, the values refer to n (%). Study drug-related adverse events in MedDRA Version 24.0 were considered as adverse reactions. The ratios (%) were calculated in the safety analysis set. For totalizing the frequencies of preferred terms, when an adverse event developed multiple times in a patient, the event was counted only once. For totalizing the numbers of adverse reactions, when an adverse event developed multiple times in a patient, all of the events were counted. Adverse reactions observed until Day 377 (the last day within a period until Week 52) are included.
Q●W: an X-week interval

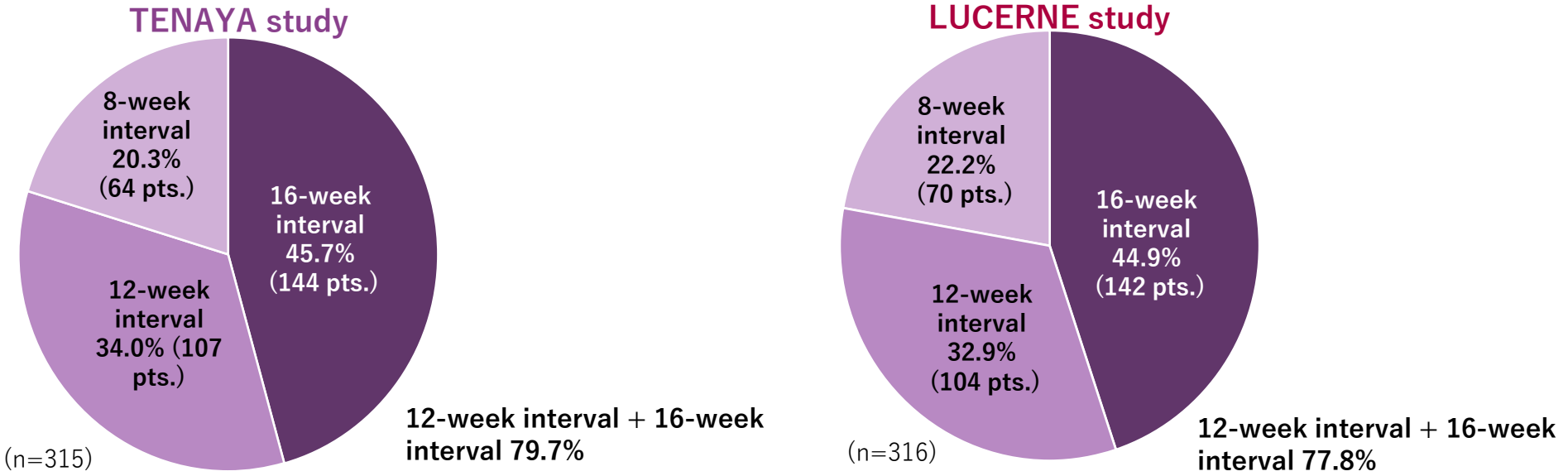
1) Evaluation material for approval: Global phase III study (GR40306 [TENAYA] study); 2) Evaluation material for approval: Overseas phase III clinical study (GR40844 [LUCERNE] study);
3)Heier JS, et al. Lancet. 2022;399(10326):729-40.

Global phase III study (TENAYA study) | Overseas phase III study (LUCERNE study; overseas data)

Summary of TENAYA and LUCERNE Studies

- In TENAYA and LUCERNE studies, improvements on visual acuity in the groups treated with Vabysmo at 8- to 16-week intervals were not inferior to the group treated with aflibercept at an 8-week interval.
- In both TENAYA and LUCERNE studies, over 40% and 70% of patients achieved the 16-week and 12- week dosing intervals, respectively.
- In TENAYA and LUCERNE studies, adverse events in the study eye that occurred at a frequency of 0.5% or greater in the Vabysmo group included intraocular inflammation (such as uveitis), increased intraocular pressure, and retinal pigment epithelial tears.

Secondary endpoint: Percentage of patients per dosing interval at 48 weeks for Vabysmo



1) Evaluation material for approval: Global phase III study (GR40306 [TENAYA] study); 2) Evaluation material for approval: Overseas phase III clinical study (GR40844 [LUCERNE] study);
3)Heier JS, et al. Lancet. 2022;399(10326):729-40.

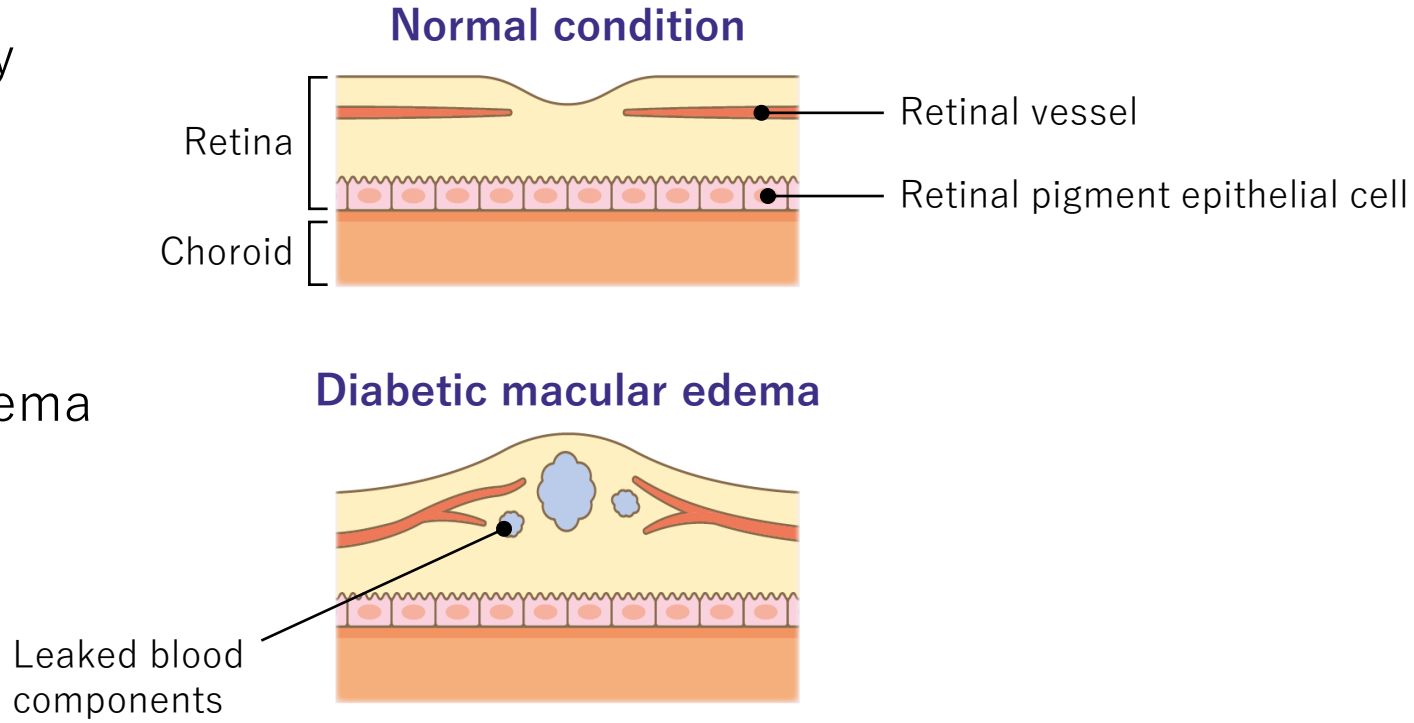
A disease causing reduced vision due to macular edema related to hyperglycemia

Diabetic Macular Edema　(DME)

What Is Diabetic Macular Edema (DME)?

- **A disease which causes reduced vision due to macular edema related to hyperglycemia.**
  - Diabetic retinopathy may develop by retinal vascular disorder due to diabetes mellitus.
  - Diabetic macular edema (DME) is a condition complicated by diabetic retinopathy that causes macular edema leading to reduced vision.

[conceptual illustration]

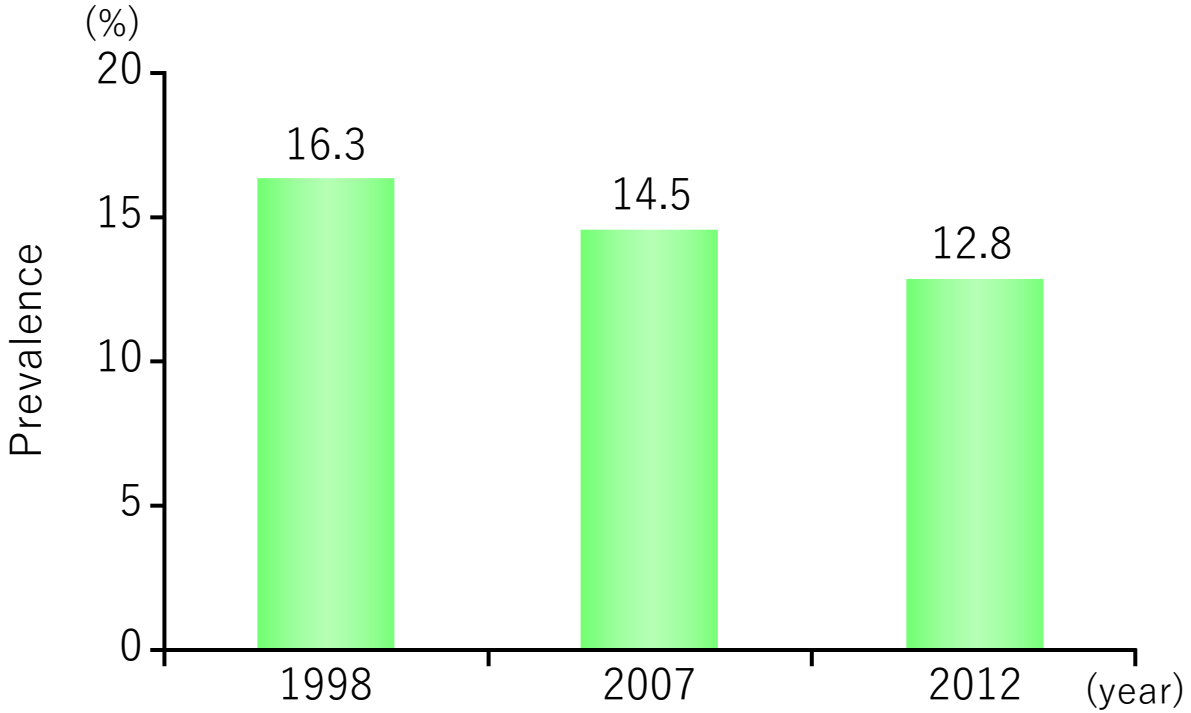


Supervising editor: Professor Makoto Inoue, Department of Ophthalmology, Kyorin University School of Medicine

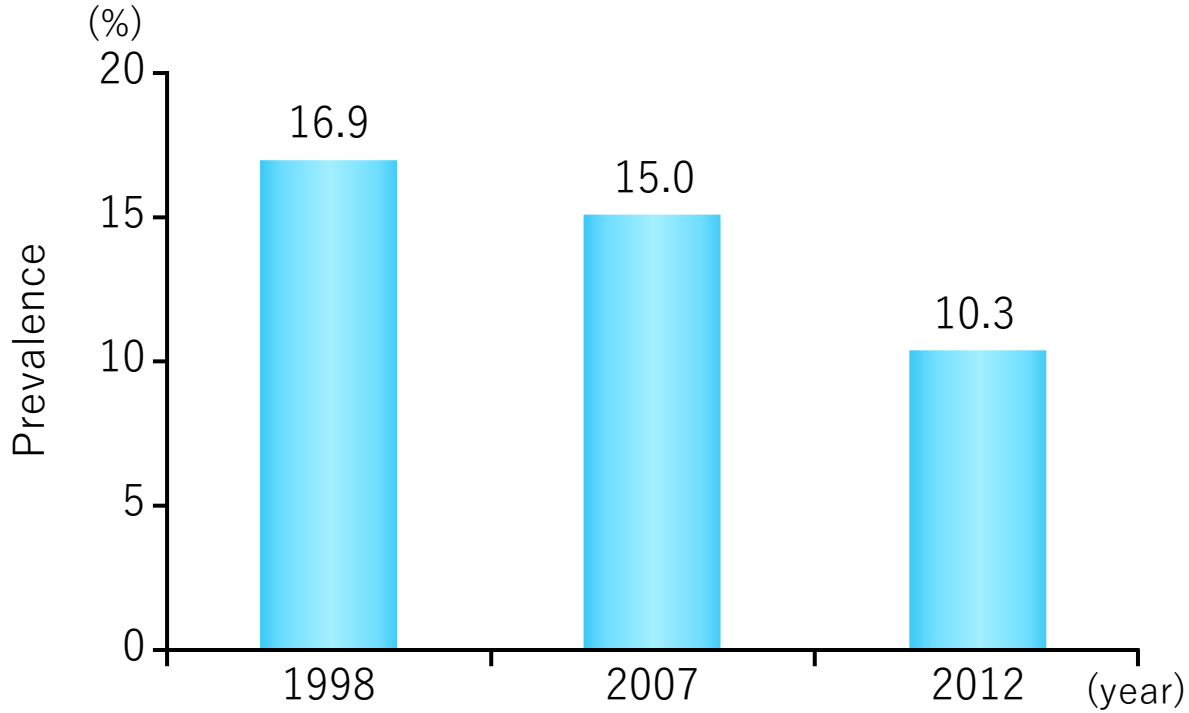
Prevalence of Diabetes Mellitus and Diabetic Retinopathy

- **In recent years, the prevalence of diabetic retinopathy has been declining in diabetic patients.**

Prevalence of diabetes mellitus in Japan



Prevalence of diabetic retinopathy in diabetic patients in Japan



Subjects and methods: A 75-g oral glucose tolerance test and funduscopy were conducted in local residents aged 40 to 79 in Hisayama-machi, Kasuya-gun, Fukuoka, Japan, and 1,637 subjects who completed both examinations were followed up.

1) Yasuda. M. Journal of the Eye. 2016;33: 1247-51.
2) Miyazaki M, et al. Diabetologia. 2004; 47: 1411-5.

Primary Diseases Considered as Visual Disorders

- **Diabetic retinopathy remains the third most common cause of visual disorder* in Japan.**

	Primary disease	Ratio (n = 12,505)
1st	Glaucoma	28.6%
2nd	Retinitis pigmentosa	14.0%
3rd	Diabetic retinopathy	12.8%
4th	Macular dystrophy (including age-related macular degeneration)	8.0%

Subjects and methods: Surveillance of age, sex, primary disease, and grade of visual disorder was conducted via welfare offices across Japan in 12,505 patients newly determined as visually impaired persons aged 18 and older (observational cross-sectional study).

*Definition of a visually impaired person:

A person who has the following permanent visual disorders shall be considered as a visually impaired person.

1. Visual acuity (a value measured in accordance with international visual acuity measurement standards. In patients with refractive error, it refers to a measurement of corrected vision. The same hereafter) of 01. or less in both eyes
2. Visual acuity of 0.02 or less in an eye and 0.6 or less in the other eye
3. Visual fields in both eyes within 10 degrees each
4. A loss of vision in half of the visual field of both eyes

The following reference was used to create the above table: 1) Morizane Y, et al. Jpn J Ophthalmol. 2019; 63:26-33. 2) Laws and regulations related to Act on Welfare of Physically Disabled Persons on the website of the Ministry of Health, Labour and Welfare (excerpt) https://www.mhlw.go.jp/file/05-Shingikai-12201000-Shakaiengokyokushougaihokenfukushibu-Kikakuka/0000149291.pdf (accessed on November 2, 2021)

Symptoms of DME*

- DME* affects the center of the visual field and impairs the vision with some symptoms including blurred vision, reduced vision, metamorphopsia, and loss of contrast sensitivity.

Metamorphopsia	Blurred vision	Loss of contrast sensitivity
Visual distortion	Cloudy vision	Difficulty in seeing objects without substantial difference in the color density and contrast.

*DME: diabetic macular edema

1) Japan Ophthalmologists Association http://www.gankaikai.or.jp/health/35/index.html (accessed on March 23, 2022)
2) Information for the general public edited by the Japanese Journal of Ophthalmology Eye diseases: Age-related macular degeneration https://www.nichigan.or.jp/public/disease/name.html?pdid=52 (accessed on March 23, 2022)

Examinations and Diagnosis of DME*

- **Retinal condition is examined by some procedures such as interview, visual acuity test, funduscopy, and optical coherence tomography.**

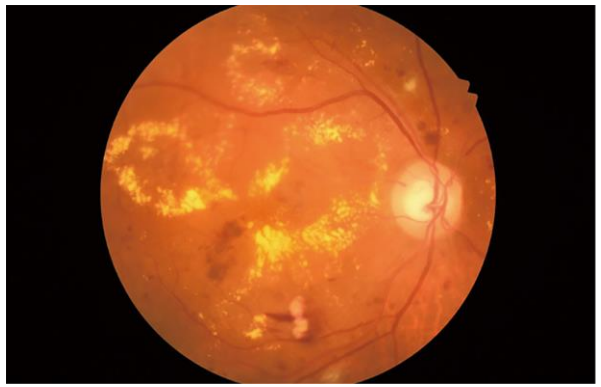
Funduscopy

- Color fundus photography: shall be conducted to obtain images of the macula lutea and the surrounding area.
- Fluorescein angiography: examines conditions with neovascularization and/or leakage of blood/blood components after injection of a contrast agent into the arm vessel.

Optical coherence tomography

- Optical coherence tomography (OCT): confirms macular conditions by obtaining cross-sectional images of the retina.

Color fundus photograph of DME*



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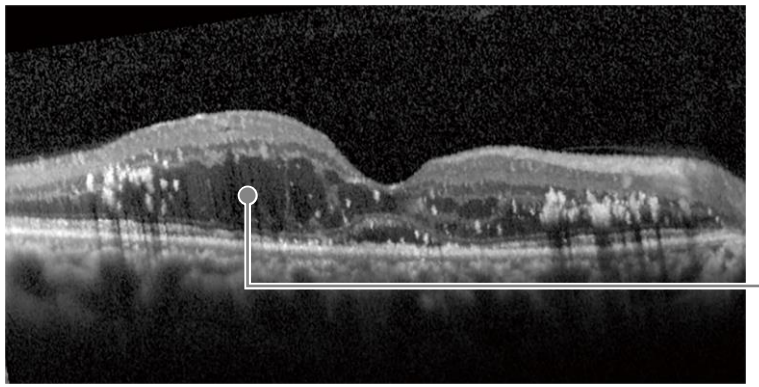
Department of Ophthalmology, Kyorin University School of Medicine

A cross-sectional image of the retina with DME* by OCT**



Supervising editor: Professor Makoto Inoue,
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*DME: diabetic macular edema **OCT: optical coherence tomography

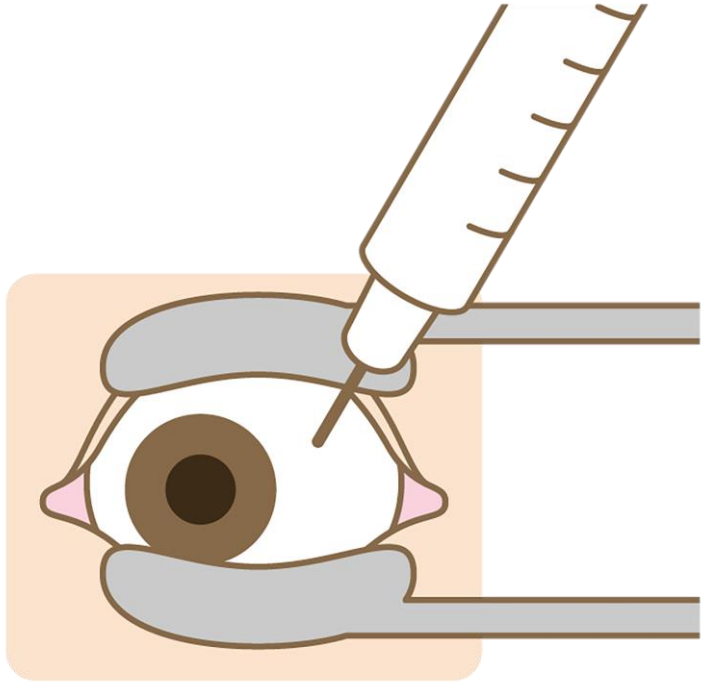
Supervising editor: Professor Ayame Annabelle Okada, Department of Ophthalmology, Kyorin University School of Medicine

Treatment of DME*

- **The basic therapy is glycemic control.**
  In addition to the basic therapy, ocular treatments include Topical ocular injection of drugs (anti-VEGF agents and steroids), laser photocoagulation, and intravitreal surgery.

Anti-VEGF intravitreal injection (anti-VEGF therapy):

- Therapy to suppress leakage of blood components from a neovessel and inflammatory edema by intraocular drug injection.
- Such treatments should be continued depending on the condition to maintain visual acuity.



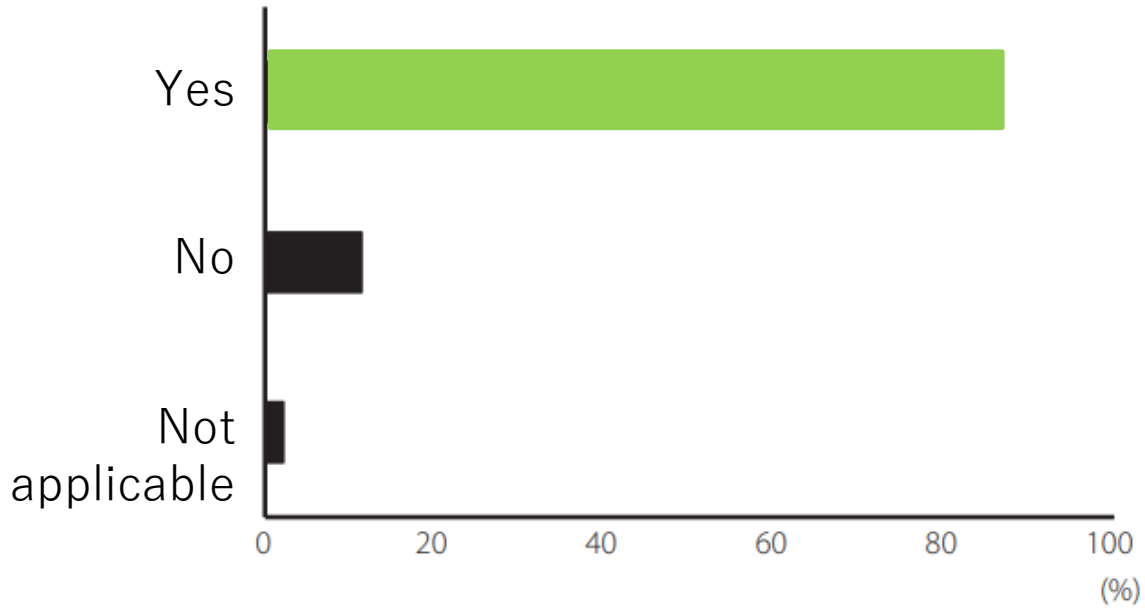
*DME: diabetic macular edema

Supervising editor: Professor Makoto Inoue, Department of Ophthalmology, Kyorin University School of Medicine

Impact of Appearance of Anti-VEGF Agents on Treatment of DME*

- **Appearance of anti-VEGF agents significantly affected the treatment of DME*.**

Question: Did anti-VEGF agents change your treatment strategy for DME?



Subjects and methods: 176 physicians treating DME in Japan were surveyed (multiple choices allowed).

Questionnaire method: Questionnaires were sent to consenting ophthalmologists from March 2016 to June 2017, and the responses obtained were tabulated.

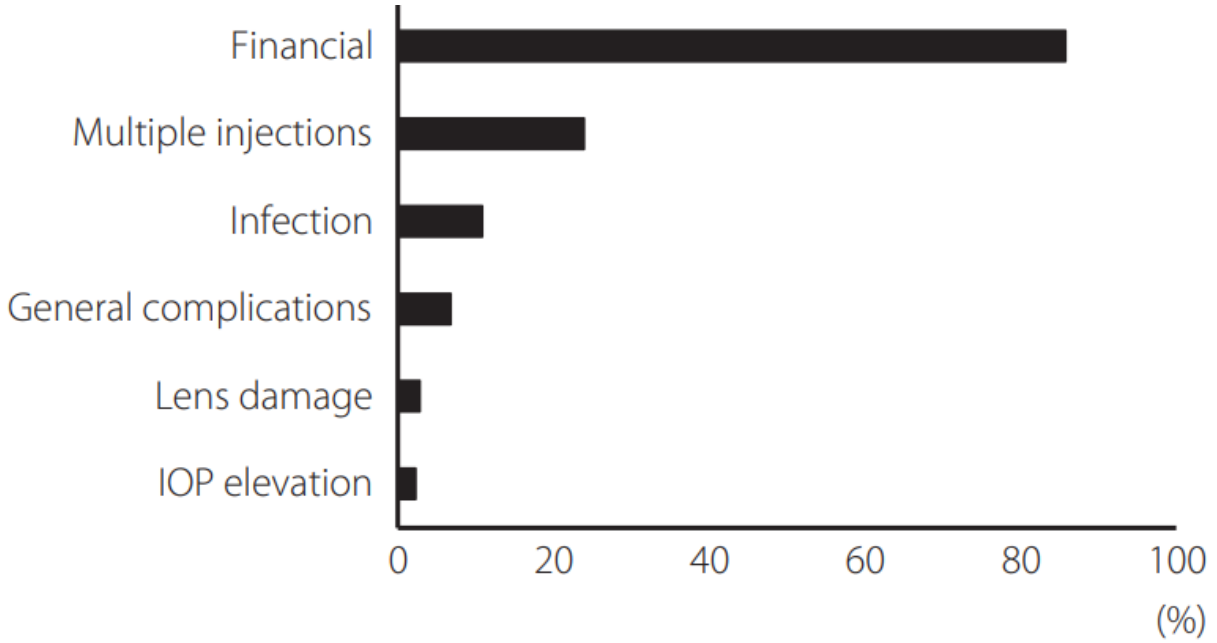
*DME: diabetic macular edema

Sugimoto M, et al. J Diabetes Investig 2019: 475-483.

Challenges for Treatment of DME* in Clinical Settings

- **The most common answer to challenges for anti-VEGF therapy was the financial burden.**

Challenges for anti-VEGF therapy for DME*



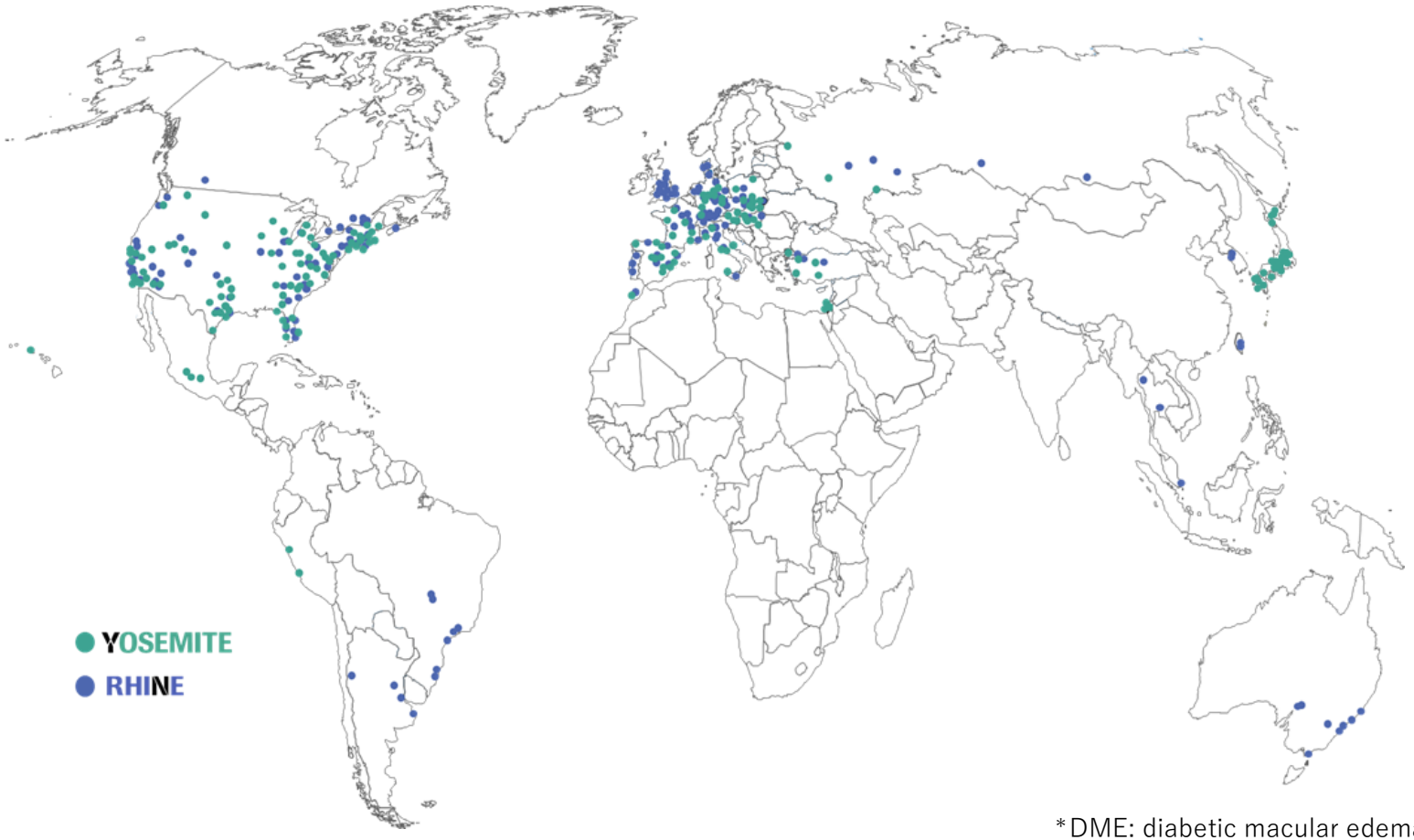
Subjects and methods: 176 physicians treating DME in Japan were surveyed (multiple choices allowed).

*DME: diabetic macular edema

Sugimoto M, et al. J Diabetes Investig 2019: 475-483.

Clinical Studies of Vabysmo in DME* (YOSEMITE and RHINE Studies)

- No. of enrolled patients: **1,891**
- No. of participating sites: **353**



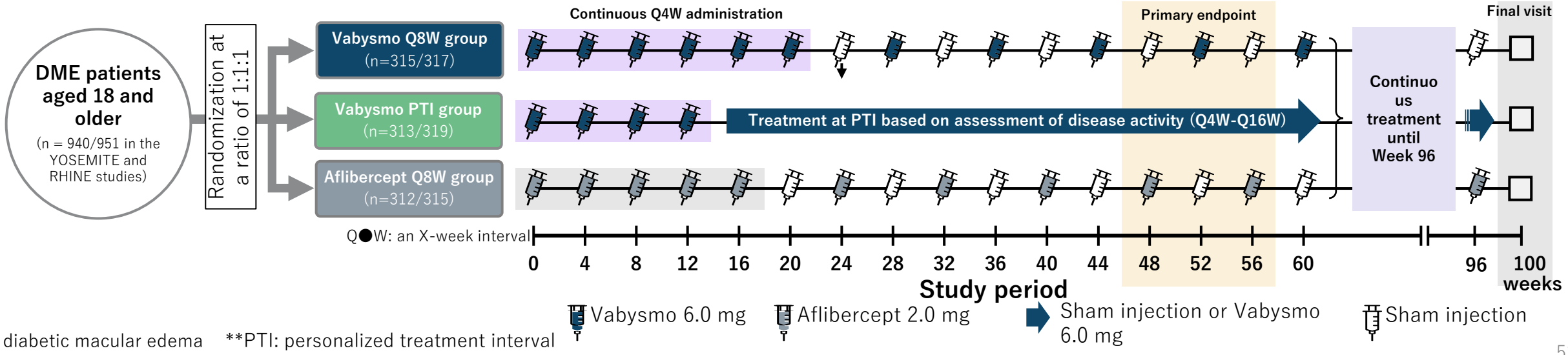
*DME: diabetic macular edema

1) Evaluation material for approval: Global phase III study (GR40349 [YOSEMITE] study); 2) Evaluation material for approval: Overseas phase III clinical trial (GR40398 [RHINE] study); 3)Wykoff CC, et al. Lancet. 2022;399(10326):741-55.

Global phase III study (YOSEMITE study) | Overseas phase III study (RHINE study; overseas data)

Study Overview: Objectives/Subjects

Study design	Multicenter, randomized, active control, double-blind, three-arm, parallel, comparative study
Subjects	Patients with DME* aged 18 and older: 940 patients (including 60 in the Japanese subgroup) in the YOSEMITE study and 951 in the RHINE study.
Dosing regimen	• Subjects shall be randomly assigned to a group administered Vabysmo at up to an 8-week interval (Q8W), Vabysmo PTI** group, or another group administered aflibercept at an 8-week interval (Q8W) at a ratio of 1:1:1. • Vabysmo Q8W group: Subjects received Vabysmo 6.0 mg at a 4-week interval until Week 20, and then at an 8-week interval until Week 96 followed by final visit at Week 100. • Vabysmo PTI** group: Subjects received Vabysmo 6.0 mg at a 4-week interval until Week 12, and then at an up to 16-week interval until Week 96 depending on the disease activity (visual acuity and central subfield thickness) followed by final visit at Week 100. • Aflibercept Q8W group: Subjects received aflibercept 2.0 mg at a 4-week interval until Week 16 and then at an 8-week interval until Week 96 followed by final visit at Week 100. • Sham injection was used to maintain blindness between groups.



*DME: diabetic macular edema **PTI: personalized treatment interval

1) Evaluation material for approval: Global phase III study (GR40349 [YOSEMITE] study); 2) Evaluation material for approval: Overseas phase III clinical trial (GR40398 [RHINE] study); 3)Wykoff CC, et al. Lancet. 2022;399(10326):741-55.

Study Overview: Endpoints

Endpoint	Efficacy	Primary endpoint (confirmatory endpoint)	**Mean values of changes in mean BCVA score (measured with ETDRS visual acuity chart) from baseline at Weeks 48, 52, and 56 (treatment-naive population)**
		The most important secondary endpoint	Ratios of patients who achieved a two-step or greater improvement from baseline in ETDRS DRSS at Week 52 (treatment-naive population)
		Key secondary endpoint	• **Time-course in mean changes in BCVA scores from baseline** • **Ratios of patients by dosing interval at Week 52 in the Vabysmo PTI group** • Ratios of patients who achieved improvement of at least 15 letters from baseline BCVA score at Weeks 48, 52, and 56 (mean) • Ratios of patients who avoided deterioration of at least 15 letters from baseline BCVA score at Weeks 48, 52, and 56 (mean) • **Mean changes in CST scores from baseline at Weeks 48, 52, and 56 and the time-course in the mean changes** • Ratios of and time-dependent changes in patients with CST of less than 325 μm (no DME observed)Note 1 at Weeks 48, 52, and 56 (mean) • Ratio of patients without intraretinal fluid at Week 52 • Ratio of patients without subretinal fluid at Week 52 • Mean changes and time-dependent changes in NEI VFQ-25 score from baseline [reference data] and others
	Key safety endpoint		• **Incidence and severity of ocular adverse events** • **Incidence and severity of non-ocular adverse events** and others

Note 1: Disappearance of DME was defined as CST of less than 325 μm with Spectralis SD-OCT, and of less than 315 μm with Cirrus SD-OCT or Topcon SD-OCT.
BCVA, best corrected visual acuity; CST, central subfield thickness; DRSS, diabetic retinopathy severity scale; ETDRS, Early Treatment Diabetic Retinopathy Study; NEI VFQ-25, National Eye Institute Visual Function Questionnaire-25; PTI, personalized treatment interval

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3)Wykoff CC, et al. Lancet. 2022;399(10326):741-55.

Global phase III study (YOSEMITE study) | Overseas phase III study (RHINE study; overseas data)

Patient Characteristics

		YOSEMITE study						RHINE study		
		ITT population			Japanese subgroup			ITT population		
		Vabysmo groups		Aflibercept Q8W group (n=312)	Vabysmo groups		Aflibercept Q8W group (n=20)	Vabysmo groups		Aflibercept Q8W group (n=315)
		Q8W group (n=315)	PTI group (n=313)		Q8W group (n=21)	PTI group (n=19)		Q8W group (n=317)	PTI group (n=319)	
Years of age, mean (SD)		61.6(9.5)	62.8(10.0)	62.2(9.6)	63.9(10.3)	63.0(10.7)	65.8(9.4)	62.5(10.1)	61.6(10.1)	62.3(10.1)
Sex, n [%]	Female	128(40.6)	116(37.1)	134(42.9)	9(42.9)	9(47.4)	9(45.0)	123(38.8)	120(37.6)	129(41.0)
HbA1c (%), mean (SD)		7.6(1.1)	7.6(1.1)	7.6(1.1)	7.2(0.6)	7.4(0.8)	7.4(0.9)	7.6(1.2)	7.7(1.2)	7.7(1.2)
Ratio of type 1 diabetes mellitus, n (%)	Yes	24(7.6)	16(5.1)	13(4.2)	1(4.8)	0	0	20(6.3)	19(6.0)	17(5.4)
Ratio of type 2 diabetes mellitus, n (%)	Yes	291(92.4)	299(95.5)	299(95.8)	21(100)	19(100)	20(100)	297(93.7)	300(94.0)	298(94.6)
BCVA score (No. of letters), mean (SD)		62.0(9.9)	61.9(10.2)	62.2(9.5)	59.3(10.9)	60.1(8.2)	59.6(8.7)	61.9(10.1)	62.5(9.3)	62.1(9.4)
CST (ILM-BM; μm), mean (SD)		492.3(135.8)	485.8(130.8)	484.5(131.1)	507.6(130.0)	478.1(123.9)	496.9(115.9)	466.2(119.4)	471.3(127.0)	477.3(129.4)
History of anti-VEGF agent IVT, n (%)	Yes	77(24.4)	68(21.7)	70(22.4)	7(33.3)	5(26.3)	5(25.0)	63(19.9)	64(20.1)	67(21.3)
	No	238(75.6)	245(78.3)	242(77.6)	14(66.7)	14(73.7)	15(75.0)	254(80.1)	255(79.9)	248(78.7)

ITT, Intention-to-treat; Q●W, an X-week interval; HbA1c, Hemoglobin A1C; BCVA, best corrected visual acuity; CST, central subfield thickness; ILM, internal limiting membrane; BM, Bruch's membrane; IVT, intravitreal

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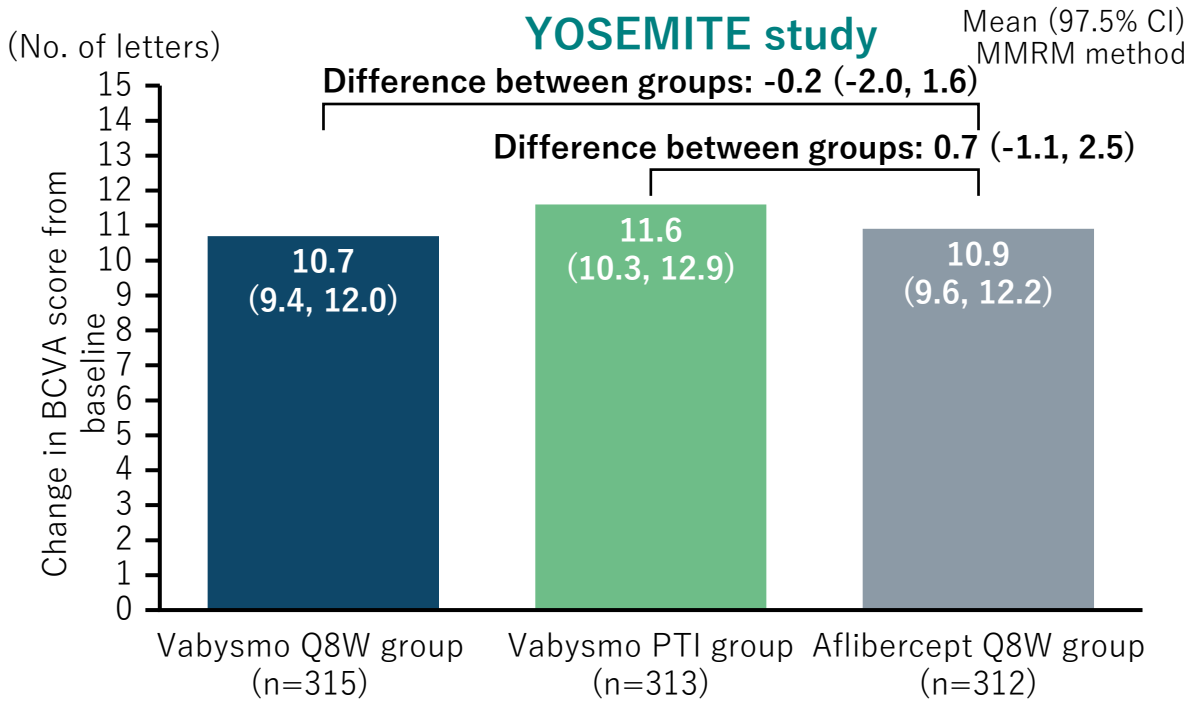
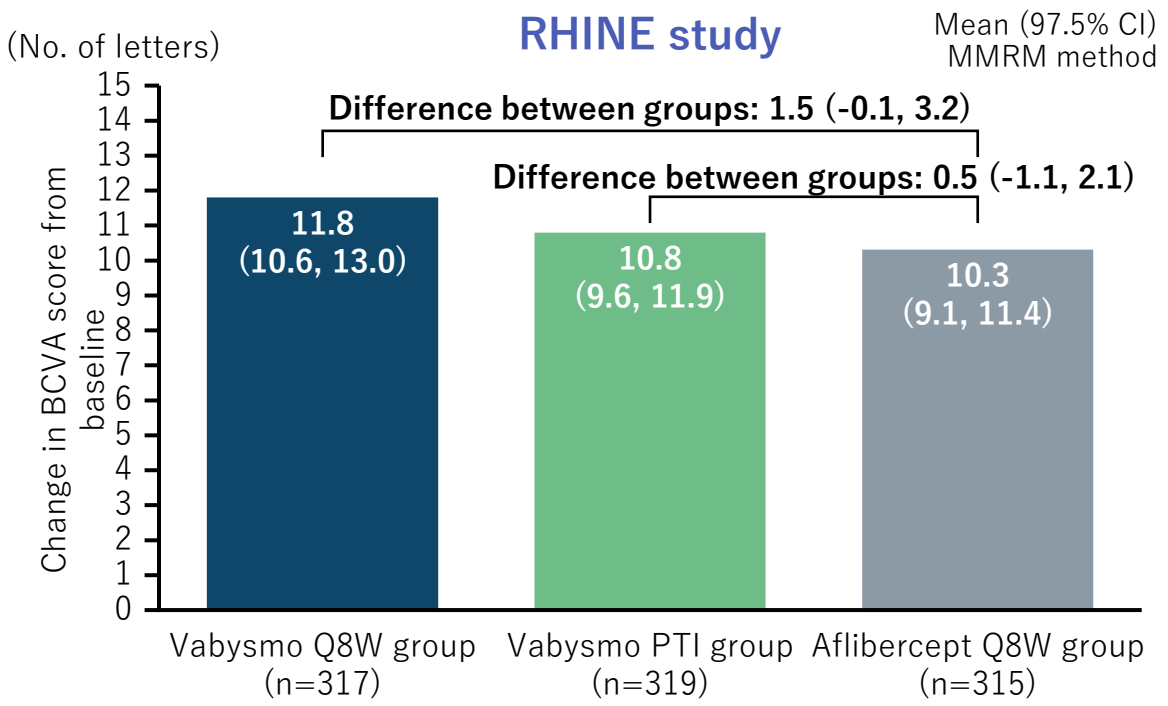
3)Wykoff CC, et al. Lancet. 2022;399(10326):741-55.

Global phase III study (YOSEMITE study) | Overseas phase III study (RHINE study; overseas data)

Primary Endpoint: Mean Change from Baseline in Mean BCVA Score at 48/52/56 Weeks

- **Non-inferiority of both Vabysmo Q8W and PTI groups to the aflibercept Q8W group was examined.**





BCVA: best corrected visual acuity　Q●W: an X-week interval　MMRM: Mixed effect Models for Repeated Measures

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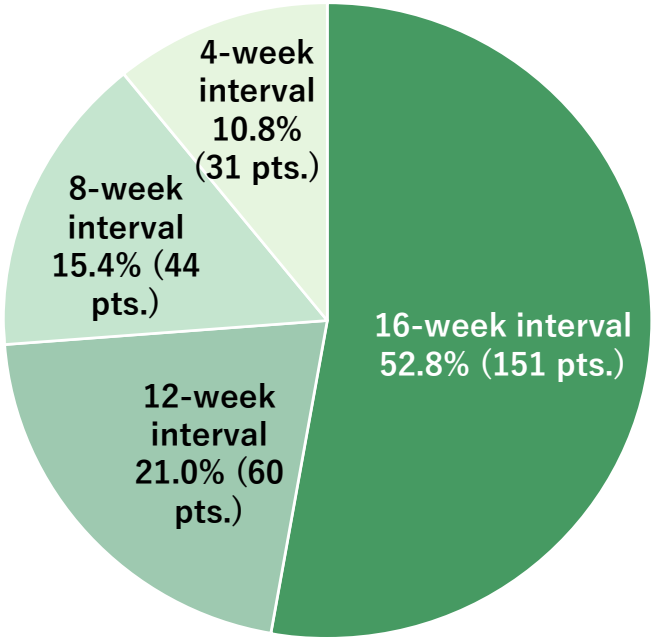
Global phase III study (YOSEMITE study) | Overseas phase III study (RHINE study; overseas data)

Secondary Endpoint: Ratios of Patients by Dosing Interval at Week 52 in the Vabysmo PTI* Group

- More than 50% and 70% of patients achieved up to 16-week and 12-week dosing intervals, respectively.

YOSEMITE study

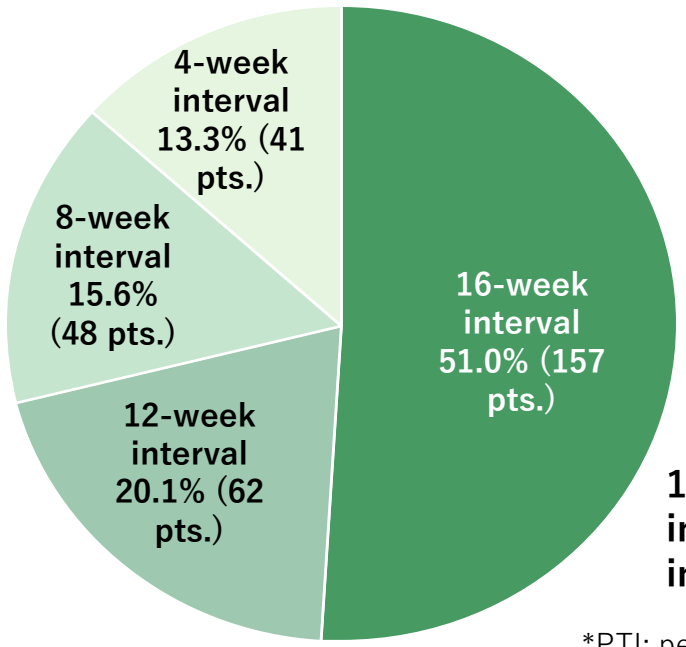
(n=286)



12-week interval + 16-week interval 73.8%

RHINE study

(n=308)



12-week interval + 16-week interval 71.1%

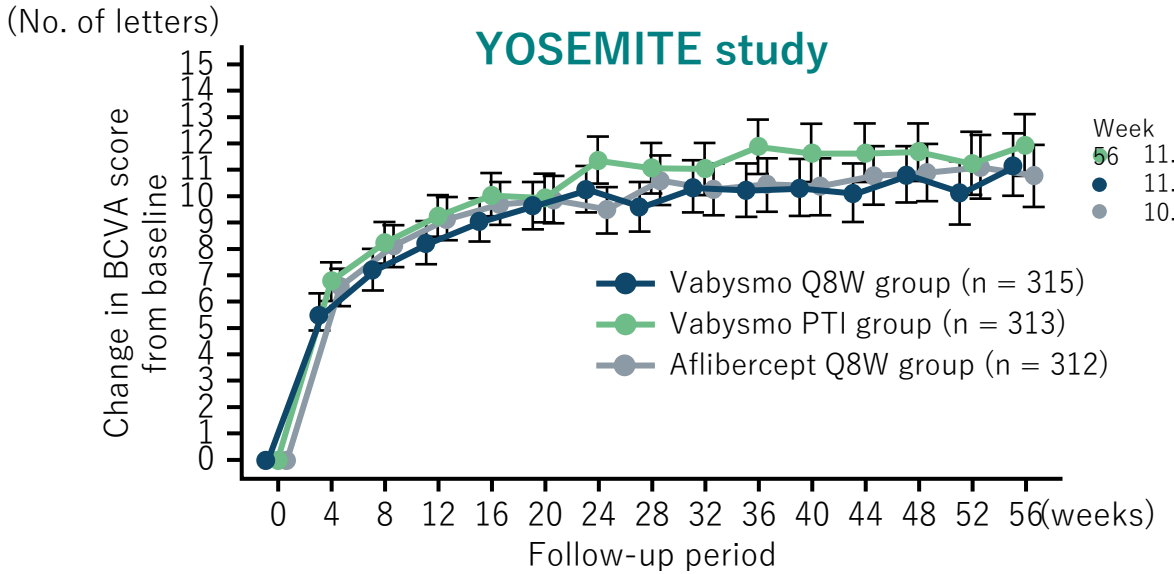
*PTI: personalized treatment interval

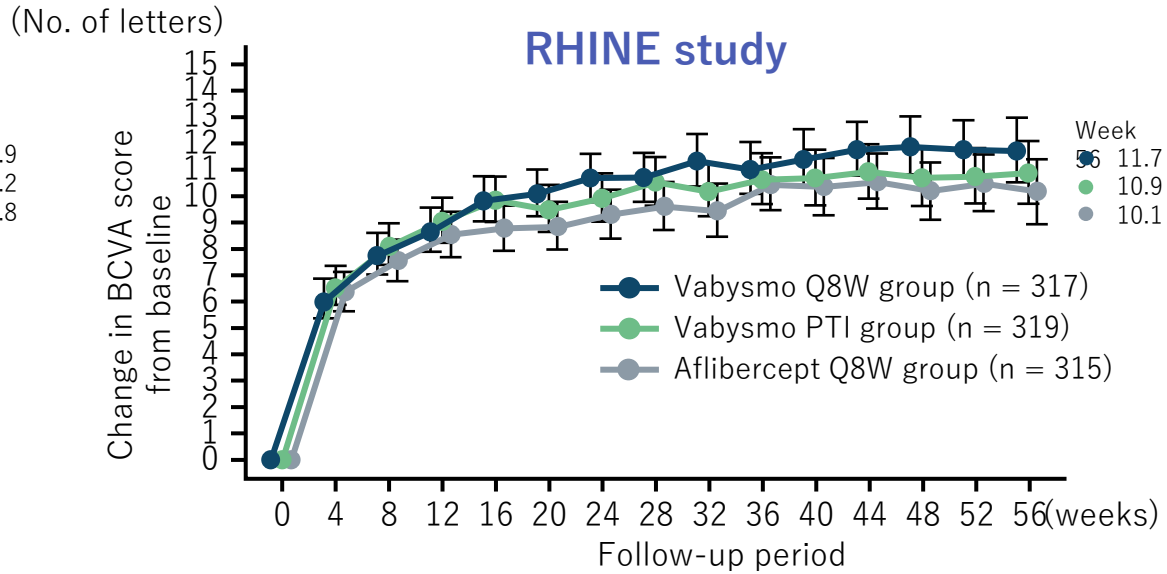
1) Evaluation material for approval: Global phase III study (GR40349 [YOSEMITE] study); 2) Evaluation material for approval: Overseas phase III clinical trial (GR40398 [RHINE] study);
3) Wykoff CC, et al. Lancet. 2022;399(10326):741-55. (conflict of interest)

Global phase III study (YOSEMITE study) | Overseas phase III study (RHINE study; overseas data)

Secondary Endpoint: Average Change from Baseline in BCVA Score

- The average change from baseline in BCVA scores was as follows.





BCVA: best corrected visual acuity
Q●W: an X-week interval

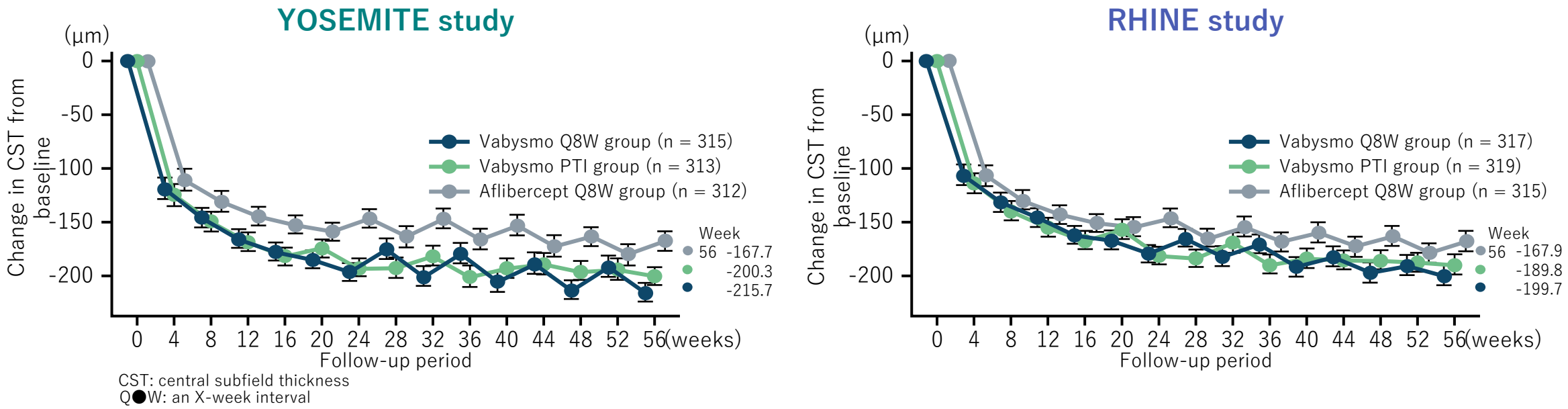
Follow-up period (week)	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56
Vabysmo Q8W group	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉
Vabysmo PTI group	💉	💉	💉	💉	Treatment at PTI (Q4W-Q16W) based on assessment of disease activity (visual acuity and central subfield thickness) →										
Aflibercept Q8W group	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉	💉
													Primary endpoint		

💉 Vabysmo 6.0 mg
💉 Aflibercept 2.0 mg
💉 Sham injection

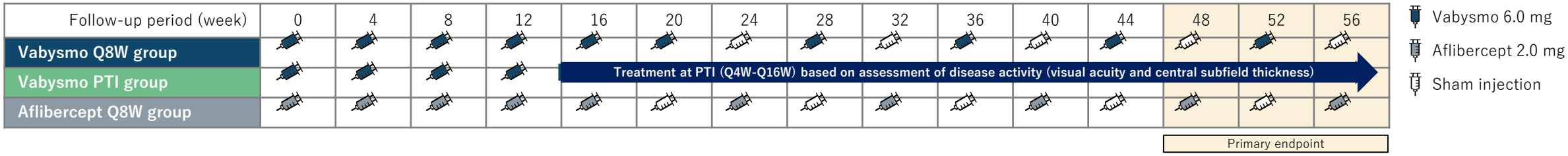
1) Evaluation material for approval: Global phase III study (GR40349 [YOSEMITE] study); 2) Evaluation material for approval: Overseas phase III clinical trial (GR40398 [RHINE] study);
3)Wykoff CC, et al. Lancet. 2022;399(10326):741-55.

Global phase III study (YOSEMITE study)　Overseas phase III study (RHINE study; overseas data)

Secondary Endpoint: Mean Change from Baseline and Mean Change in Central Retinal Thickness at 48/52/56 Weeks (ITT Population)



CST: central subfield thickness
Q●W: an X-week interval



1) Evaluation material for approval: Global phase III study (GR40349 [YOSEMITE] study);　2) Evaluation material for approval: Overseas phase III clinical trial (GR40398 [RHINE] study);
3)Wykoff CC, et al. Lancet. 2022;399(10326):741-55.

Global phase III study (YOSEMITE study) | Overseas phase III study (RHINE study; overseas data)

Safety 1: Adverse Reactions in the Study Eyes

Item name MedDRA preferred term	YOSEMITE study						RHINE study		
	Overall population			Japanese subgroup			Overall population		
	Vabysmo		Aflibercept Q8W group (n=311)	Vabysmo		Aflibercept Q8W group (n=20)	Vabysmo		Aflibercept Q8W group (n=314)
	Q8W group (n=313)	PTI group (n=313)		Q8W group (n=21)	PTI group (n=19)		Q8W group (n=317)	PTI group (n=319)	
All adverse reactions developed in the study eyes	11(3.5)	8(2.6)	5(1.6)	3(14.3)	1(5.3)	0(0.0)	8(2.5)	8(2.5)	14(4.5)
The total No. of adverse reactions developed in the study eyes	15	13	7	4	2	0	8	9	14
Intraocular pressure increased	5(1.6)	1(0.3)	1(0.3)	1(4.8)	0	0	2(0.6)	2(0.6)	3(1.0)
Vitreous floaters	2(0.6)	0	1(0.3)	0	0	0	4(1.3)	1(0.3)	3(1.0)
Uveitis	1(0.3)	3(1.0)	0	1(4.8)	1(5.3)	0	0	0	0
Cataract	0	1(0.3)	0	0	0	0	0	1(0.3)	1(0.3)
Iritis	0	2(0.6)	1(0.3)	0	0	0	0	0	0
Ocular hypertension	0	1(0.3)	0	0	0	0	0	2(0.6)	0
Vitritis	1(0.3)	0	1(0.3)	0	0	0	1(0.3)	0	0
Conjunctival hemorrhage	0	0	1(0.3)	0	0	0	0	0	1(0.3)
Diabetic retinal edema	1(0.3)	0	0	0	0	0	0	0	1(0.3)
Eye pain	1(0.3)	0	0	0	0	0	0	0	1(0.3)

Unless otherwise specified, the values refer to n (%). Drug-related adverse events in MedDRA Version 23.1 were considered as adverse reactions. The ratios (%) were calculated in the safety analysis set. For totalizing the frequencies of preferred terms, when an adverse event developed multiple times in a patient, the event was counted only once. For totalizing the numbers of adverse reactions, when an adverse event developed multiple times in a patient, all of the events were counted. Adverse events observed until Day 405 (the last day within a period until Week 56) are included.

Q●W: an X-week interval

1) Evaluation material for approval: Global phase III study (GR40349 [YOSEMITE] study); 2) Evaluation material for approval: Overseas phase III clinical trial (GR40398 [RHINE] study);
3)Wykoff CC, et al. Lancet. 2022;399(10326):741-55.

Global phase III study (YOSEMITE study) | Overseas phase III study (RHINE study; overseas data)

Safety 2: Adverse Reactions in the Study Eyes (Continued)

Item name MedDRA preferred term	YOSEMITE study						RHINE study		
	Overall population			Japanese subgroup			Overall population		
	Vabysmo		Aflibercept Q8W group (n=311)	Vabysmo		Aflibercept Q8W group (n=20)	Vabysmo		Aflibercept Q8W group (n=314)
	Q8W group (n=313)	PTI group (n=313)		Q8W group (n=21)	PTI group (n=19)		Q8W group (n=317)	PTI group (n=319)	
Keratitis	0	0	0	0	0	0	0	1(0.3)	1(0.3)
Chorioretinitis	0	1(0.3)	0	0	0	0	0	0	0
Corneal abrasion	0	0	0	0	0	0	1(0.3)	0	0
Corneal edema	0	1(0.3)	0	0	0	0	0	0	0
Keratic precipitates	0	1(0.3)	0	0	1(5.3)	0	0	0	0
Keratouveitis	0	1(0.3)	0	0	0	0	0	0	0
Macular fibrosis	1(0.3)	0	0	1(4.8)	0	0	0	0	0
Ocular discomfort	0	0	0	0	0	0	0	1(0.3)	0
Vision blurred	0	0	0	0	0	0	0	0	1(0.3)
Visual impairment	0	0	0	0	0	0	0	0	1(0.3)
Vitreous detachment	0	0	0	0	0	0	0	0	1(0.3)

Unless otherwise specified, the values refer to n (%). Drug-related adverse events in MedDRA Version 23.1 were considered as adverse reactions. The ratios (%) were calculated in the safety analysis set. For totalizing the frequencies of preferred terms, when an adverse event developed multiple times in a patient, the event was counted only once. For totalizing the numbers of adverse reactions, when an adverse event developed multiple times in a patient, all of the events were counted. Adverse events observed until Day 405 (the last day within a period until Week 56) are included.

Q●W: an X-week interval

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3)Wykoff CC, et al. Lancet. 2022;399(10326):741-55

Global phase III study (YOSEMITE study) | Overseas phase III study (RHINE study; overseas data)

Safety 3: Non-Ocular Adverse Reactions

Item name MedDRA preferred term	YOSEMITE study						RHINE study		
	Overall population			Japanese subgroup			Overall population		
	Vabysmo		Aflibercept	Vabysmo		Aflibercept	Vabysmo		Aflibercept
	Q8W group (n=313)	PTI group (n=313)	Q8W group (n=311)	Q8W group (n=21)	PTI group (n=19)	Q8W group (n=20)	Q8W group (n=317)	PTI group (n=319)	Q8W group (n=314)
All non-ocular adverse reactions	3(1.0)	1(0.3)	0(0.0)	0(0.0)	1(5.3)	0(0.0)	1(0.3)	2(0.6)	2(0.6)
The total No. of adverse reactions developed in the study eyes	3	1	0	0	1	0	1	2	2
Nervous system disorders	1(0.3)	0	0	0	0	0	1(0.3)	1(0.3)	1(0.3)
Cerebrovascular accident	0	0	0	0	0	0	0	0	1(0.3)
Ischemic stroke	1(0.3)	0	0	0	0	0	0	0	0
Lacunar stroke	0	0	0	0	0	0	0	1(0.3)	0
Headache	0	0	0	0	0	0	1(0.3)	0	0
Cardiac disorders	0	0	0	0	0	0	0	0	1(0.3)
Acute myocardial infarction	0	0	0	0	0	0	0	0	1(0.3)
Vascular disorders	1(0.3)	0	0	0	0	0	0	0	0
Hypertension	1(0.3)	0	0	0	0	0	0	0	0
Ear and labyrinth disorders	0	1(0.3)	0	0	1(5.3)	0	0	0	0
Sudden hearing loss	0	1(0.3)	0	0	1(5.3)	0	0	0	0
Psychiatric disorders	1(0.3)	0	0	0	0	0	0	0	0
Visual hallucinations	1(0.3)	0	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	0	0	1(0.3)	0
Rhinorrhea	0	0	0	0	0	0	0	1(0.3)	0

Unless otherwise specified, the values refer to n (%). Drug-related adverse events in MedDRA Version 23.1 were considered as adverse reactions. The ratios (%) were calculated in the safety analysis set. For totalizing the frequencies of preferred terms, when an adverse event developed multiple times in a patient, the event was counted only once. For totalizing the numbers of adverse reactions, when an adverse event developed multiple times in a patient, all of the events were counted. Adverse events observed until Day 405 (the last day within a period until Week 56) are included.

Q●W: an X-week interval

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Global phase III study (YOSEMITE study) | Overseas phase III study (RHINE study; overseas data)

Occurrences of Adverse Reactions Related to Intraocular Inflammation

- **In a combined analysis of both studies, adverse reactions related to intraocular inflammation were observed in 9 subjects of the overall Vabysmo group and 2 in the aflibercept Q8W group.**

		YOSEMITE study			RHINE study			Overall DME*			
		Vabysmo		Aflibercept Q8W group (n=311)	Vabysmo		Aflibercept Q8W group (n=314)	Vabysmo			Aflibercept Q8W group (n=625)
		Q8W group (n=313)	PTI group (n=313)		Q8W group (n=317)	PTI group (n=319)		Q8W group (n=630)	PTI group (n=632)	Overall (n=1262)	
Adverse Reactions		2(0.6)	6(1.9)	2(0.6)	1(0.3)	0	0	3(0.5)	6(0.9)	9(0.7)	2(0.3)
Serious adverse reaction other than death		0	4(1.3)	0	0	0	0	0	4(0.6)	4(0.3)	0
Severity	Mild	0	2(0.6)	2(0.6)	1(0.3)	0	0	1(0.2)	2(0.3)	3(0.2)	2(0.3)
	Moderate	1(0.3)	4(1.3)	0	0	0	0	1(0.2)	4(0.6)	5(0.4)	0
	Severe	1(0.3)	2(0.6)	0			0	1(0.2)	2(0.3)	3(0.2)	0
Adverse reaction leading to discontinuation of treatment		1(0.3)	2(0.6)	0	0	0	0	1(0.2)	2(0.3)	3(0.2)	0

Unless otherwise specified, the values refer to n (%). MedDRA version 23.1 * Integrated data from the YOSEMITE and RHINE studies. Study drug-related adverse events were considered as adverse reactions. The ratios (%) were calculated in the safety analysis set. For totalizing the frequencies of preferred terms, when an adverse event developed multiple times in a patient, the event was counted only once. For totalizing the numbers of adverse reactions, when an adverse event developed multiple times in a patient, all of the events were counted. Adverse reactions observed until Day 405 (the last day within a period until Week 56) are included.

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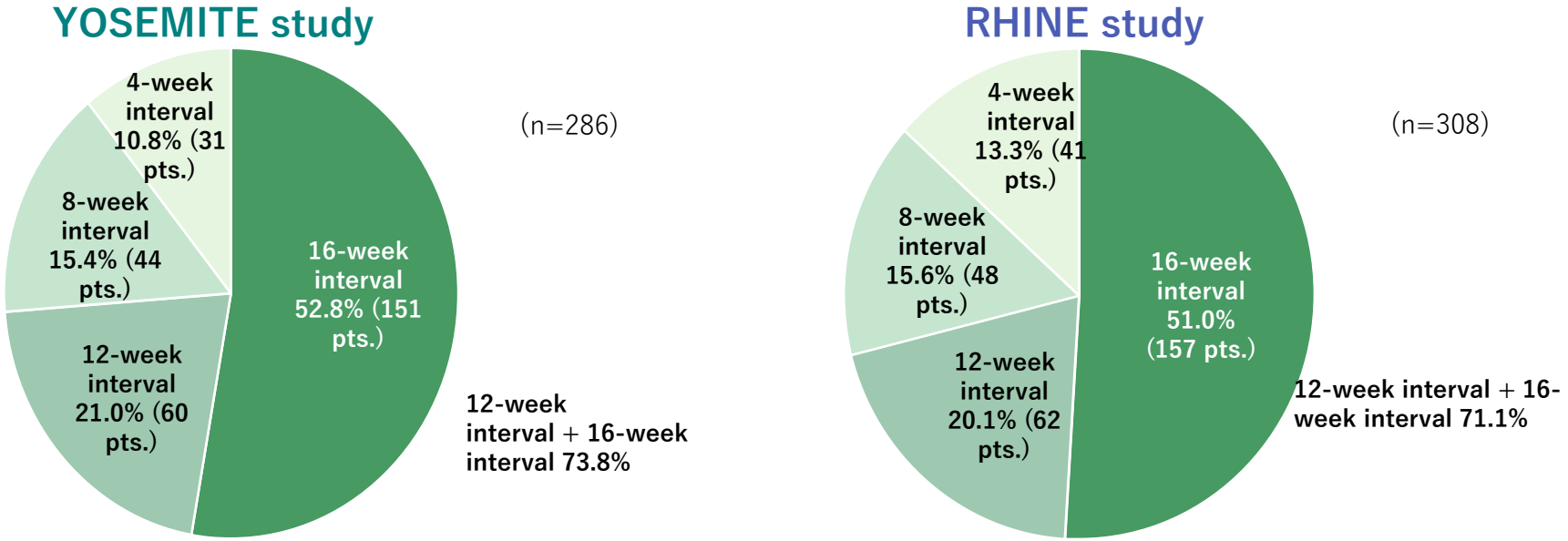
Global phase III study (YOSEMITE study) | Overseas phase III study (RHINE study; overseas data)

Summary of the YOSEMITE and RHINE Studies

- In the YOSEMITE and RHINE studies, improvement of visual acuity in the Vabysmo PTI group at up to a 16-week interval was not inferior to the aflibercept group at an 8-week interval.
- In both the YOSEMITE and RHINE studies, more than 50% and 70% of patients achieved the 16-week and 12-week dosing intervals, respectively.
- In the YOSEMITE and RHINE studies, adverse events in the study eye that occurred at a frequency of 0.5% or greater in the Vabysmo group included intraocular inflammation (such as uveitis), increased intraocular pressure, and vitreous floaters.

Secondary endpoint: Percentage of patients per dosing interval at 48 weeks for Vabysmo



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VABYSMO Solution for Intravitreal Injection 120 mg/mL
Generic name: Faricimab

Package
0.24 mL × 1 vial
（one filter needle for withdrawal of injection solution attached)

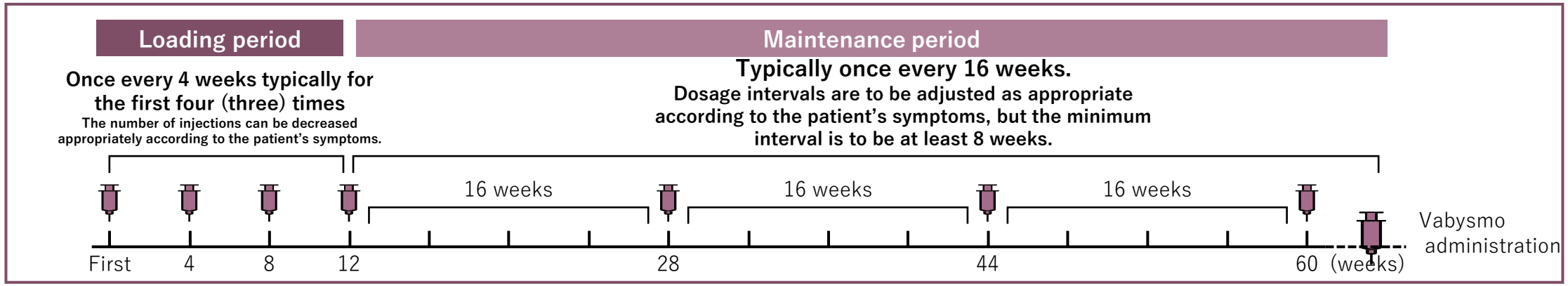
Indications
○ Age-related macular degeneration associated with subfoveal choroidal neovascularization
○ Diabetic macular edema

Digitalized Package Insert of Vabysmo Solution for Intravitreal Injection 120 mg/mL (March 2022; Version 1)

Dosage and Administration (Age-Related Macular Degeneration Associated With Subfoveal Choroidal Neovascularization)

Dosage and administration

6 mg (0.05 mL) of faricimab (genetical recombination) is administered by intravitreal injection once every 4 weeks typically for the first four times (loading period), but the number of injections can be reduced appropriately according to the patient's symptoms. In the subsequent maintenance period, it is typically administered by intravitreal injection once every 16 weeks. Dosage intervals are to be adjusted as appropriate according to the patient's symptoms, but the minimum interval is to be at least 8 weeks.



7. Precautions Concerning Dosage and Administration (excerpt)

7.1 Binocular treatments are not conducted during clinical studies. When both eyes have lesions to be treated, carefully assess the benefits and risks associated with simultaneous treatment of both eyes before administering VABYSMO. Avoid administration of VABYSMO to both eyes on the same day during initial treatment; evaluate safety after administering VABYSMO to one eye before administering VABYSMO to the opposite eye.

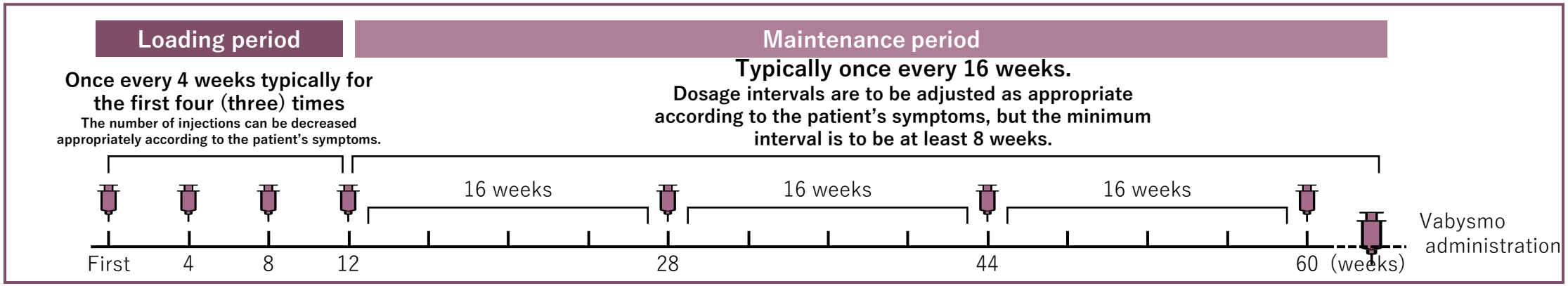
7.2 Regarding the frequency of treatment during the loading period, consider the administration of intravitreal injection once every 4 weeks for the first three times according to the assessment of disease activity as appropriate. During the maintenance period, consider a dosing interval of e.g. 8 or 12 weeks if any findings of disease activity are observed.

Digitalized Package Insert of Vabysmo Solution for Intravitreal Injection 120 mg/mL (March 2022; Version 1)

Dosage and Administration (Age-Related Macular Degeneration Associated With Subfoveal Choroidal Neovascularization)

Dosage and administration

6 mg (0.05 mL) of faricimab (genetical recombination) is administered by intravitreal injection once every 4 weeks typically for the first four times (loading period), but the number of injections can be reduced appropriately according to the patient's symptoms. In the subsequent maintenance period, it is typically administered by intravitreal injection once every 16 weeks. Dosage intervals are to be adjusted as appropriate according to the patient's symptoms, but the minimum interval is to be at least 8 weeks.



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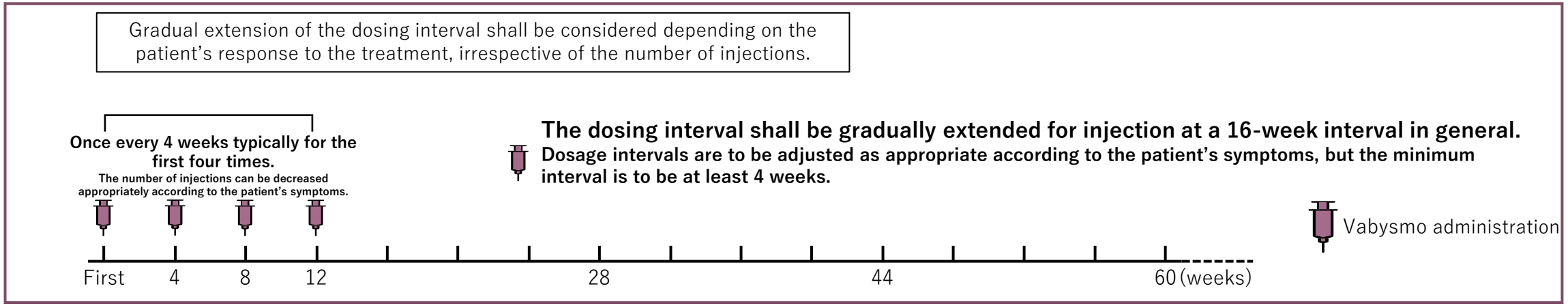
Digitalized Package Insert of Vabysmo Solution for Intravitreal Injection 120 mg/mL (March 2022; Version 1)

Dosage and Administration (Diabetic Macular Edema)

Dosage and administration

6 mg (0.05 mL) of faricimab (genetical recombination) is administered by intravitreal injection once every 4 weeks typically for the first four times, but the number of injections can be reduced appropriately according to the patient's symptoms. Subsequently, it is typically administered by intravitreal injection once every 16 weeks after gradually extending the dosing interval. Dosage intervals are to be adjusted as appropriate according to the patient's symptoms, but the intervals are to be at least 4 weeks.



7. Precautions Concerning Dosage and Administration (excerpt)

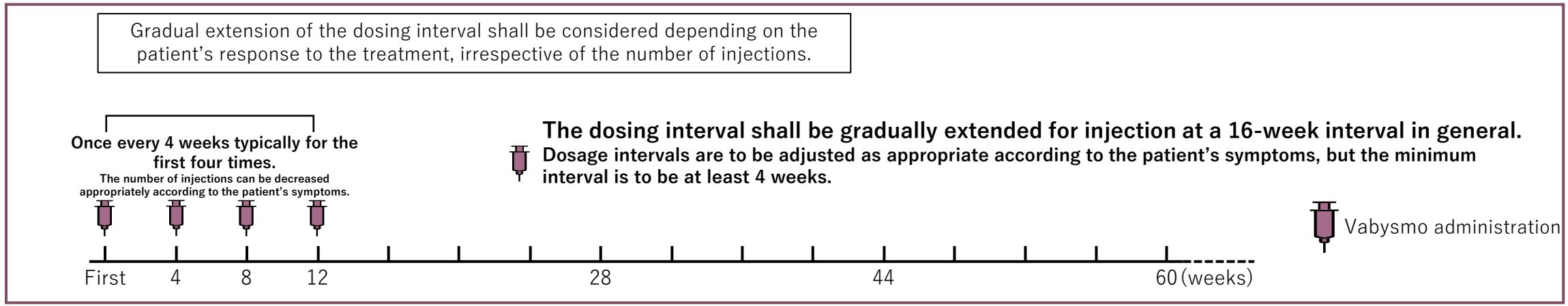
7.1 Binocular treatments are not conducted during clinical studies. When both eyes have lesions to be treated, carefully assess the benefits and risks associated with simultaneous treatment of both eyes before administering VABYSMO. Avoid administration of VABYSMO to both eyes on the same day during initial treatment; evaluate safety after administering VABYSMO to one eye before administering VABYSMO to the opposite eye.

7.3 After starting the treatment, consider extending the treatment interval gradually according to the treatment response, regardless of the number of injections. Then, monitor the disease activity on a regular basis and consider a dosing interval of e.g. 4, 8 and 12 weeks if any findings of disease activity are observed.

Dosage and Administration (Diabetic Macular Edema)

Dosage and administration

6 mg (0.05 mL) of faricimab (genetical recombination) is administered by intravitreal injection once every 4 weeks typically for the first four times, but the number of injections can be reduced appropriately according to the patient's symptoms. Subsequently, it is typically administered by intravitreal injection once every 16 weeks after gradually extending the dosing interval. Dosage intervals are to be adjusted as appropriate according to the patient's symptoms, but the intervals are to be at least 4 weeks.



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Digitalized Package Insert of Vabysmo Solution for Intravitreal Injection 120 mg/mL (March 2022; Version 1)

Adverse Reactions

Adverse Reactions

The following adverse reactions may occur. Carefully monitor patients, and if any abnormalities are observed, take appropriate measures, which may include the discontinuation of treatment.

Clinically Significant Adverse Reactions

Eye disorders

Intraocular inflammation (uveitis, vitritis, etc.) (1.0%), retinal pigment epithelial tears (0.4%), endophthalmitis (frequency unknown), and rhegmatogenous retinal detachment and retinal tears (frequency unknown) may occur. There have been reports of recurrence of intraocular inflammation after re-administration to patients with intraocular inflammation due to VABYSMO treatment. [see 8.3.5]

Stroke

Ischemic stroke (0.05%), Thrombotic cerebral infarction (0.05%), and lacunar stroke (0.05%) may occur. [see 9.1.2 and 15.1.1]

Other Adverse Reactions

	Less than 1%	Frequency unknown
Eye disorders	Intraocular pressure increased, vitreous floaters, ocular hypertension, corneal abrasion, eye pain, ocular discomfort	Conjunctival hemorrhage

Digitalized Package Insert of Vabysmo Solution for Intravitreal Injection 120 mg/mL (March 2022; Version 1)

Expectations for Vabysmo

- With the therapeutic efficacy based on a novel mechanism of action, Vabysmo may become a new treatment option for patients who cannot be adequately treated with existing treatments.
- Due to the sustained efficacy of Vabysmo, longer dosing intervals can be expected during the maintenance period.
- The extended dosing interval may potentially reduce the burden of hospital visits for patients and their accompanying caregivers.
- Adverse reactions should be further monitored.

Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends.

Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

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INNOVATION BEYOND IMAGINATION