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CHUGAI PHARMACEUTICAL CO., LTD.

Information Meeting on Vabysmo

June 24, 2022

Event Summary

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[Venue]	Webcast
[Venue Size]	
[Participants]	

[Number of Speakers]	3	
	Masashi Kishida	Vabysmo Lifecyle Leader
	Tomohiro Iida	Professor and Chairman, Department of Ophthalmology, Tokyo Women's Medical University
	Toshiya Sasai	Head of Corporate Communications Department
[Analyst Names]*	Fumiyoshi Sakai	Credit Suisse Securities (Japan) Limited
	Hidemaru Yamaguchi	Citigroup Global Markets Japan Inc.
	Kazuaki Hashiguchi	Daiwa Securities Co. Ltd.
	Shinichiro Muraoka	Morgan Stanley MUFG Securities Co., Ltd.

*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A.

Presentation

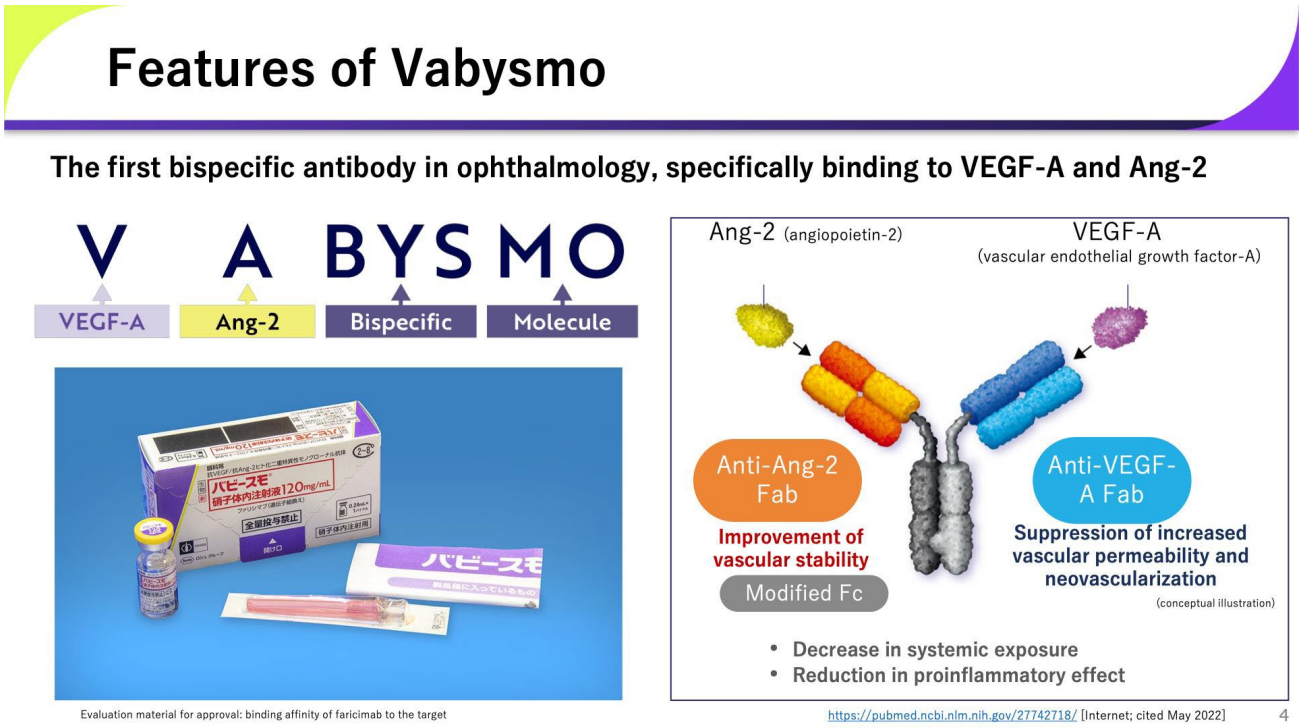
Sasai: Hello. Thank you very much for taking time out of your busy schedule today to attend the product presentation of our new ophthalmologic treatment, Vabysmo.

I'm Sasai of the Corporate Communications Department, and I'll be moderating today's session. Thank you.

To prevent the spread of novel coronavirus infection, today's session will be conducted as a combination of an on-site lecture and a Zoom webinar. The agenda for today's meeting can be found on the web page and on page two of the presentation material. Please follow the contents of this page.

Today, we have invited as a special lecturer, Dr. Tomohiro Iida, Professor and Chairman, Department of Ophthalmology, Tokyo Women's Medical University. Dr. Iida's biography, along with today's presentation materials, have been distributed in advance. I would like to skip the biography in this presentation. We kindly ask for your understanding. Questions will be taken collectively after all presentations have been completed. The Q&A session is scheduled to last about 30 minutes.

I would now like to turn the session over to Dr. Kishida, Vabysmo Lifecycle Leader.

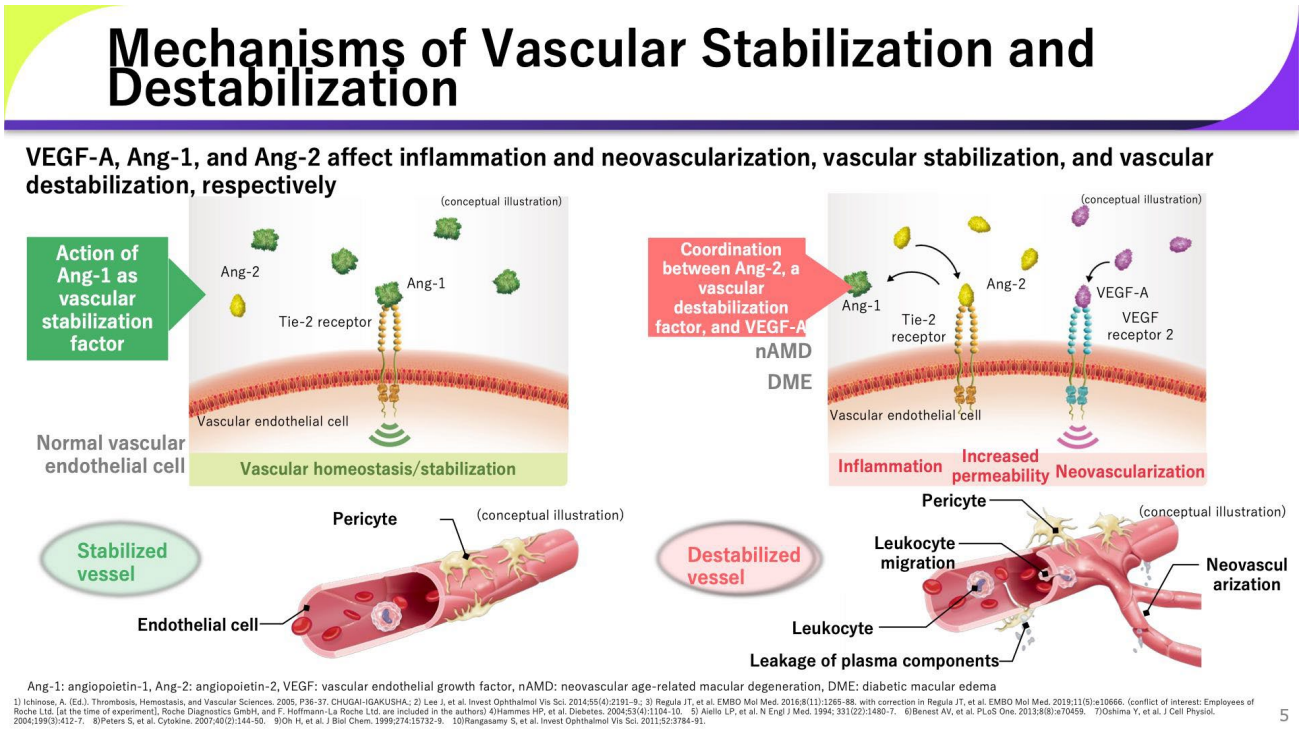


Kishida: My name is Kishida. I'm the Vabysmo Lifecycle Leader of CHUGAI PHARMACEUTICAL CO., LTD. Thank you for attending today's presentation.

First, let me give you a product overview of the Vabysmo Intravitreal Injection solution. Here is a slide showing the features of Vabysmo. Vabysmo is the first bispecific antibody in the ophthalmologic field that specifically binds to vascular endothelial growth factor A, a molecule called VEGF-A, and Ang-2.

The English spelling of Vabysmo is thus: V stands for VEGF-A, A for Ang-2, BYS for Bispecific, and MO for Molecule. Vabysmo binds not only VEGF-A but also Ang-2, two cytokines, at the same time, and is expected

to improve vascular stability, increase vascular permeability, and inhibit angiogenesis. The Fc domain, which is the area connecting the two Fabs, has been modified to reduce systemic exposure and inflammation induction.



Next, I will briefly discuss the mechanisms of vascular stabilization and destabilization.

VEGF-A is inflammation and angiogenesis, the molecule called Ang-1 is vascular stabilizing, a good thing, and Ang-2 is vascular destabilizing a bad factor. In normal vascular endothelial cells, Ang-1 binds to Tie-2 receptors and generates signals that stabilize the pericytes lining the vessels, thereby maintaining and stabilizing vascular homeostasis.

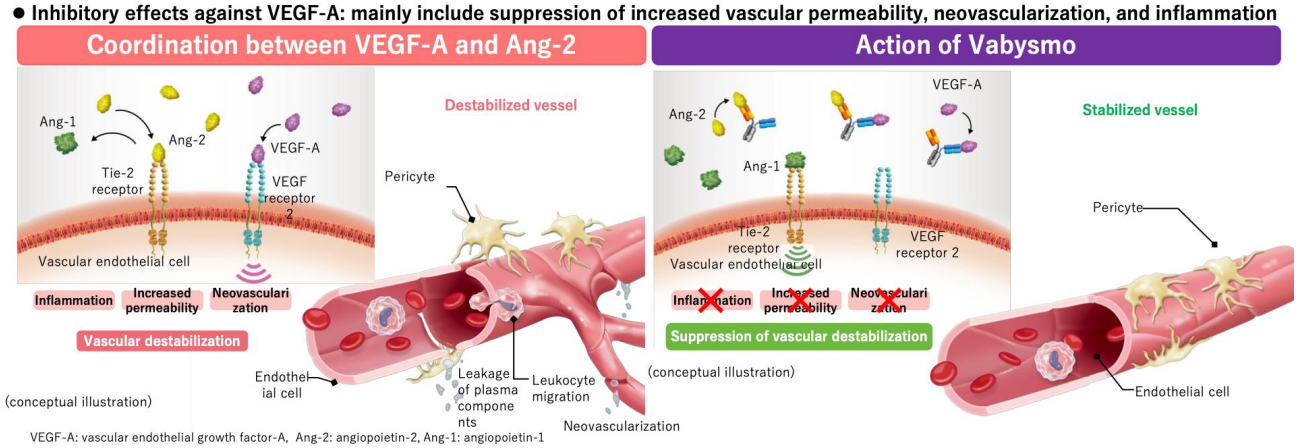
It is known that Ang-2 and VEGF-A are simultaneously elevated in the eyes of patients with age-related macular degeneration and diabetic macular edema due to destabilization. Ang-2 acts as an antagonist to Ang-1, removing Ang-1 from the Tie-2 receptor and stopping this stabilizing signal by binding Ang-2 to the receptor.

At the same time, a molecule called VEGF-A binds to VEGF receptor 2 and generates signaling, which in total increases inflammation, permeability, and angiogenesis. The patient's vision is then said to be reduced by the occurrence of destabilized blood vessels due to leakage of plasma components, pericyte detachment, and angiogenesis.

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**



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.

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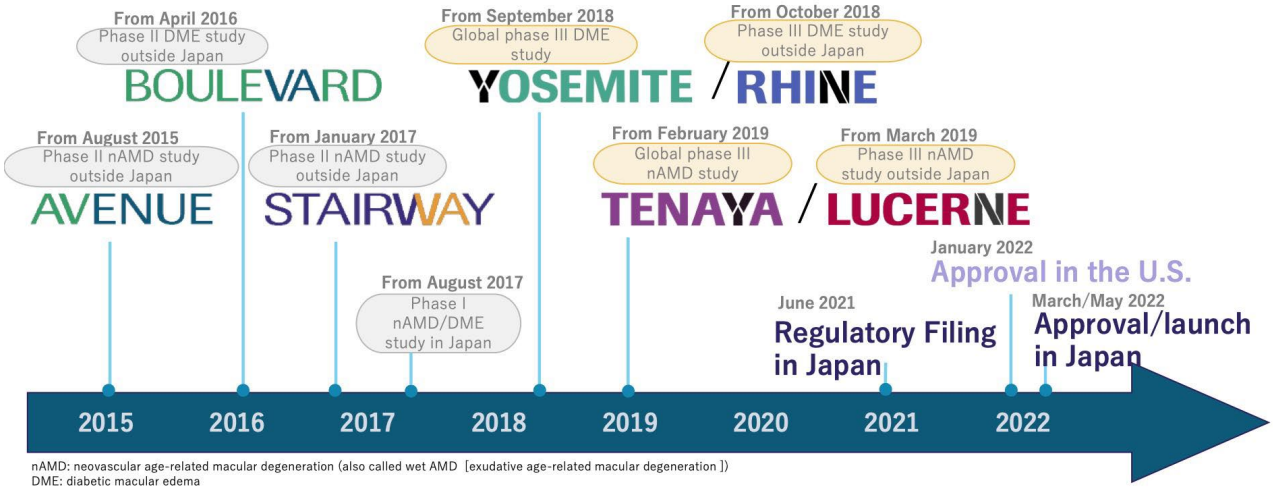
Vabysmo can inhibit VEGF-A and Ang-2 simultaneously with this single molecule. By simultaneously trapping increased Ang-2 and VEGF-A in the patient's eye, the Ang-2 inhibitory effect works primarily to suppress vascular destabilization due to pericyte loss, increased vascular permeability, and increased VEGF-A sensitivity. At the same time, by inhibiting VEGF-A, it is believed to suppress increased vascular permeability, angiogenesis, and inflammation, thereby contributing to the improvement of patients' visual acuity.

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

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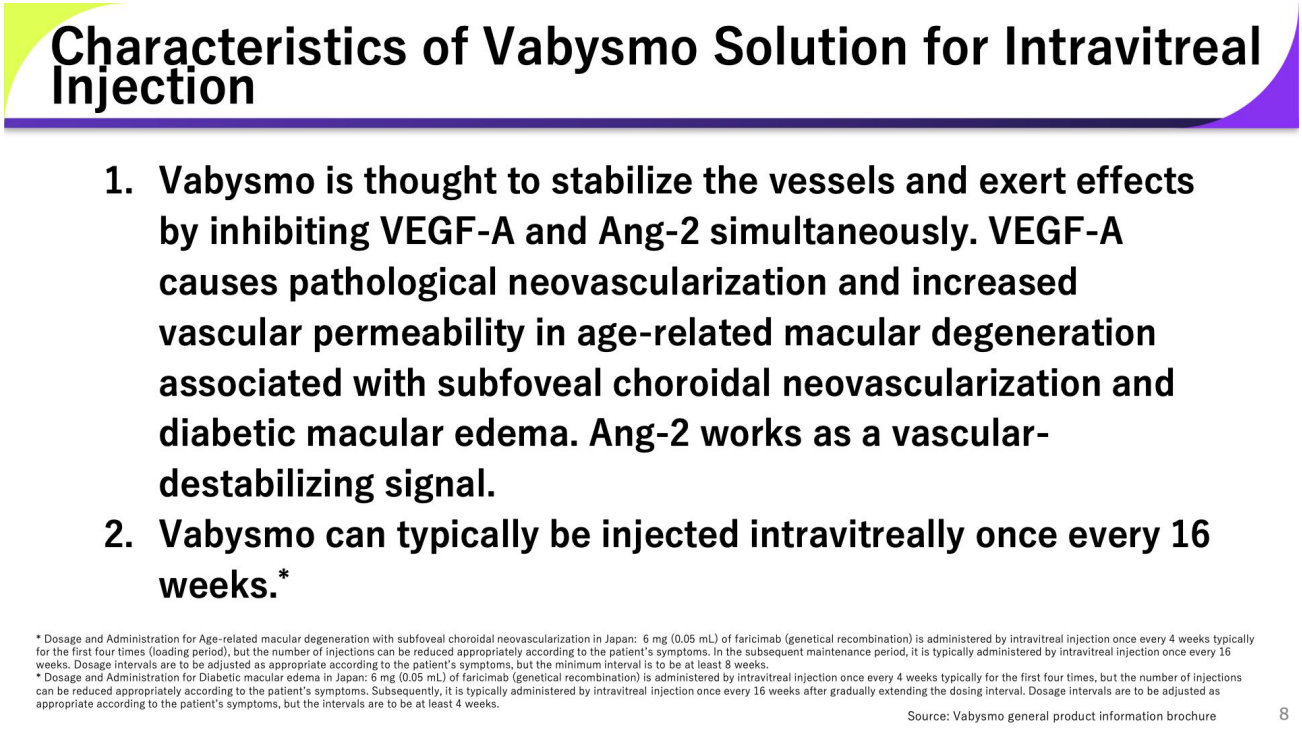
Next, I would like to highlight the development history of Vabysmo. Vabysmo had been developed for two indications: age-related macular degeneration with subfoveal choroidal neovascularization and diabetic macular edema.

In June 2021, both indications were submitted for approval for domestic use. For age-related macular degeneration, we conducted two Phase II studies called AVENUE and STAIRWAY, and additionally two more Phase III studies called TENAYA/LUCERNE, for diabetic macular edema, we conducted an overseas Phase II study called BOULEVARD and the Phase III study called YOSEMITE/RHINE. In March of this year, we obtained regulatory approval on both indications for Vabysmo, making Japan the second country worldwide after the U.S. We launched the product in May 2022.



This is the slide, which describes the characteristics of Vabysmo solution for intravitreal injection.

In addition to VEGF-A, which causes pathological angiogenesis and increased vascular permeability in age-related macular degeneration associated with subfoveal choroidal neovascularization and diabetic macular edema, Ang-2, which acts as a vascular destabilizing signal, is thought to be stabilized and effective by simultaneously inhibiting Ang-2.

As for dosage and administration, the details will be explained later, but it is usually possible to administer intravitreally once every 16 weeks.

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)

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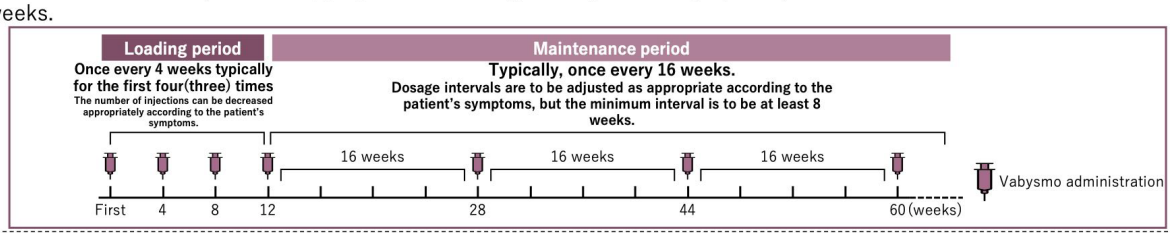
Here are the indications. Let me skip them for now as they will be redundant. I would like to note the primary reminder of this medication. Avoid facile administration of this medication to patients as it may not be effective to for all patients. In package insert, precautions concerning indications say that when starting treatment using Vabysmo, take into consideration the patient's prognosis, such as visual acuity, before deciding whether Vabysmo treatment is necessary.

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.

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

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Here, first, are the dosage and administration for age-related macular degeneration associated with subfoveal choroidal neovascularization. It is stated that 6 mg (0.05 mL) of faricimab is administered by intravitreal

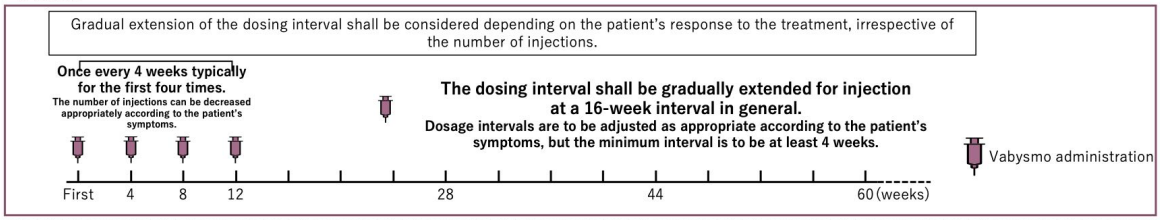
injection once every 4 weeks typically for the first four times (loading period), but the number of injections can be reduced appropriately according to the patient's symptoms.. In the subsequent maintenance period, it is typically administered by intravitreal injection once every 16 weeks. Dosage intervals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

As a reminder, since 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. The number of doses may be reduced accordingly depending on this symptom. In the frequency of treatment during the loading period, four doses may be reduced to three according to the assessment of disease activity. In the maintenance period, the usual interval is every 16 weeks, but 8 weeks or 12 weeks may also be considered depending on the patient's diseaseactivity.

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.

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

Next comes the dosage and administration in diabetic macular edema.

Similarly, the medication 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.

In the case of binocular administration, the same precautions as for age-related macular degeneration have been taken, and in terms of the dosing interval, regardless of the number of doses given-four, three, two, or one at the beginning of the administration, the interval can be gradually extended in accordance with the therapeutic response.

Even if the dosing interval is extended to 16 weeks, if the patient's disease activity is observed, the dosing interval of 4, 8, or 12 weeks will be considered.

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

Digitalized Package Insert of Vabysmo Solution for Intravitreal Injection 120 mg/mL (March 2022; Version 1) 12

Next will be the adverse reactions.

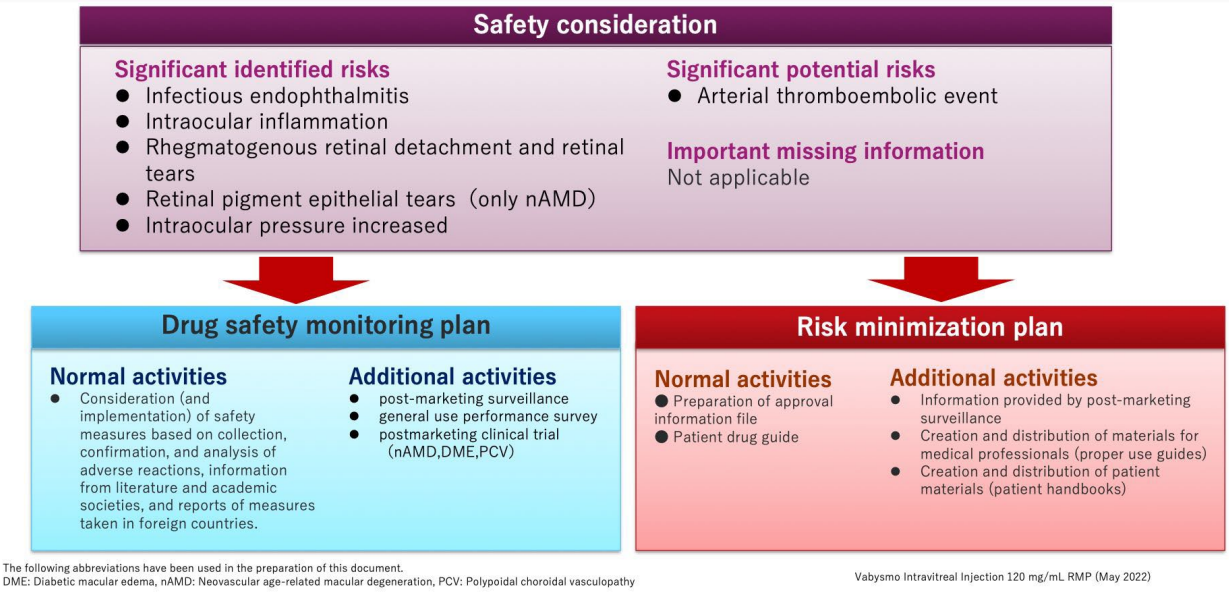
clinically significant adverse reactions include intraocular inflammation, retinal pigment epithelial tear, endophthalmitis, rhegmatogenous retinal detachment, and retinal tear.

In addition, there have been reports of cases of recurrence of intraocular inflammation in patients who had intraocular inflammation following administration of the medication, so doctors are advised to use the medication with caution.

Systemic adverse reactions include ischemic stroke, thrombotic cerebral infarction, and lacunar stroke.

Other adverse reactions include intraocular pressure increased, vitreous floaters, ocular hypertension, corneal abrasions, eye pain, ocular discomfort, and conjunctival hemorrhage.

Vabysmo Intravitreal Injection 120 mg/mL Risk Management Plan



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

Vabysmo Intravitreal Injection 120 mg/mL RMP (May 2022)

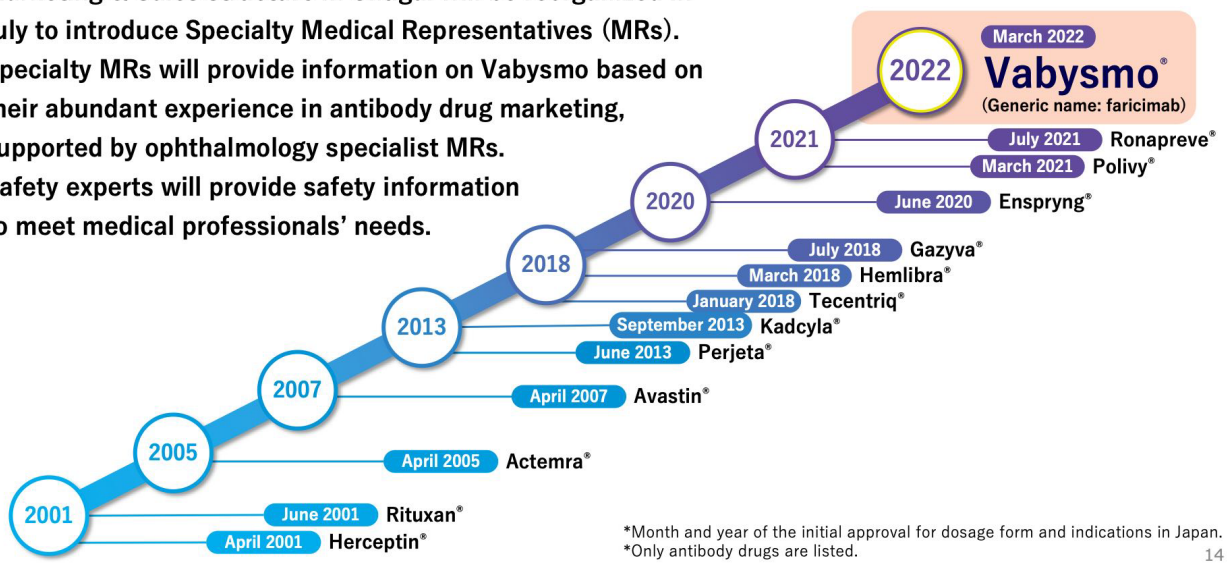
For each of these identified, significant potential risks, a risk management plan, known as an RMP, is prepared.

In this safety consideration, as part of the medication safety monitoring plan, the first step is to collect information on adverse reactions, and additional activities such as post-marketing surveillance, general use performance survey, and post-marketing clinical trials are also planned.

To plan for minimizing these risks, in addition to the usual package inserts and patient-oriented drug guides, information is intended to be provided through post-marketing surveillance. In addition, we have prepared and distributed proper use guides for medical professionals and patient materials.

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.

As we are entering the ophthalmology field for the first time, we are currently building an internal system to provide more advanced value.

In July 2022, we plan to reorganize our sales structure to take the form of a specialty MR structure. In addition, Chugai has a track record of marketing many antibody drugs, starting with Herceptin and Rituxan in 2001, and including Actemra, Avastin, Tecentriq, Hemlibra, Enspryng, Polivy, and Ronapreve.

Therefore, we are planning to develop information provision activities for Vabysmo by deploying and supporting MRs specializing in ophthalmology in addition to these specialty MRs, taking advantage of their abundant experience in sales of this antibody medication.

We also consider the provision of safety information to be extremely important and have assigned safety experts to provide safety information to meet the needs of medical professionals.

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]

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We have launched an informative website, "Ever visible.jp (Japanese only)", for patients. In addition, it is said that it is very important these days to extend the healthy life span of the eye, which is called eye frailty, and we plan to include this eye frailty activity in the future, as well as other information for various patients and their families on this site.

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

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The final slide summarizes Vabysmo. Vabysmo is the first bispecific antibody in the ophthalmologic field that specifically binds to these two VEGF-A and Ang-2. Approved and launched for two indications simultaneously. Dosage and administration are once every four weeks in the loading period, usually four consecutive intravitreal doses, and once every 16 weeks in the maintenance period. And we are determined to provide advanced value in ophthalmology, utilizing our extensive experience in marketing antibody medications to realize better treatment.

Please note that, during my presentation, I used the technical term subfoveal choroidal neovascularization, to match the description in the package inserts. For the following presentation, I have asked Dr. Iida to use more general easy-to-understand expressions, which is exudative age-related macular degeneration.

This wraps up my presentation.

Sasai: Thank you very much. Next, Dr. Iida of Tokyo Women's Medical University will present the clinical significance of Vabysmo. Now then, Dr. Iida, please proceed.

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

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Iida: My name is Iida from Tokyo Women's Medical University. Today, I would like to talk about the clinical significance of Vabysmo. Some of my content may overlap with what Dr. Kishida mentioned earlier, but I hope you will consider it an important matter. This is my conflict of interest.

I will give an overview of the two types of disease, age-related macular degeneration, and diabetic macular edema, and then I will talk about the significance of Vabysmo and, lastly, prospects.

A disease-causing reduced vision with aging

Age-Related Macular Degeneration (AMD)

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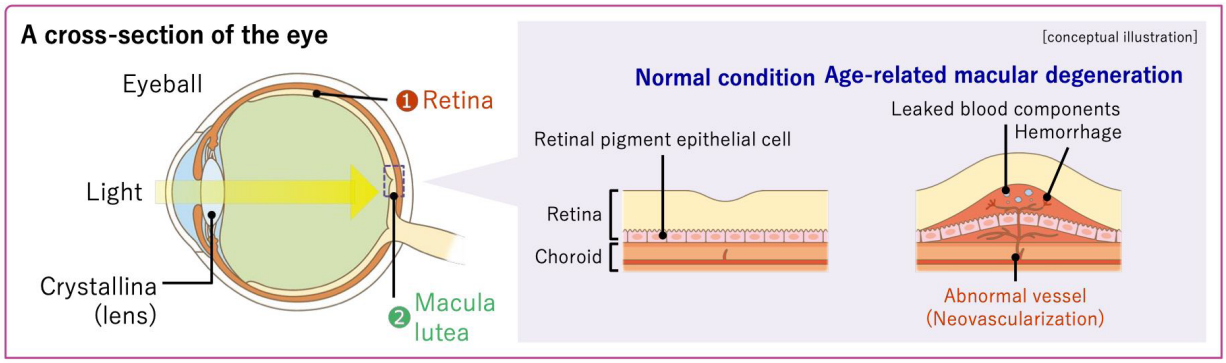
First, age-related macular degeneration. Age-related macular degeneration, or AMD for short. This disease causes age-related vision loss.

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.**



- There is a thin membrane called the "retina" behind the eye that recognizes visual information (1). "Macula lutea" at the center of the retina is a particularly important region for recognizing the shape, color, and size of an object (2).
- 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

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First, let me say a few words about the macula. This topic will appear one more time when I touch on diabetic macular edema.

The human eye's retina is where light is received, and the macula is located in the center of the retina. The retina is the tissue in the eye and sense light. The structure of the eye is such that light is concentrated here. In other words, people recognize things through the macula.

This light coming from laser pointer, you see this, your macula is working right now. While your eyes are on the light, I bet your eyes also catch me in the corner. That's because your retina, surrounding the macula, is sensing the vision. If you have just turned toward me, you are looking at me using the macula. Now look at the slide now. You see what I mean. So, when we see things, we see things in the macula, and I'd like to address the disease that occurs there.

With regard to age-related macular degeneration, ageing causes a buildup of waste products. Age-related macular degeneration is an accumulation of waste products that can cause a variety of pathological conditions. The figure on the right shows exudative age-related macular degeneration, which I will discuss later. The accumulation of waste products results in the formation of abnormal blood vessels, or neovascular vessels, from which exudation or hemorrhage damages the macula, resulting in vision loss.

Types of AMD*

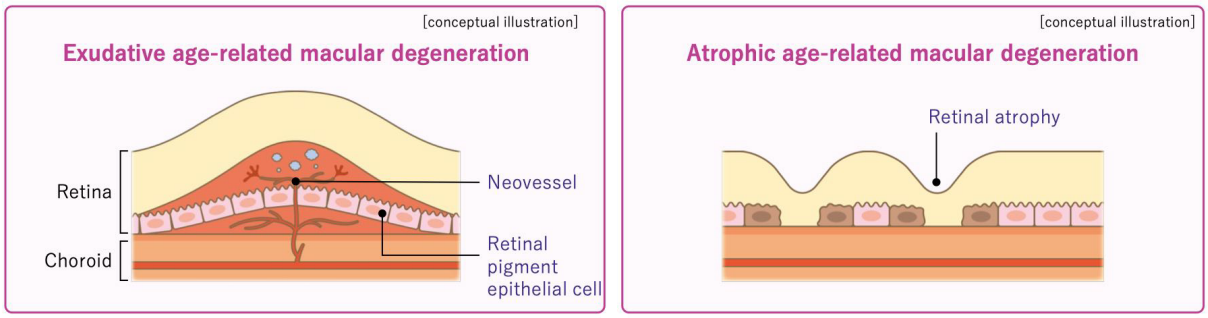
- **There are two types of conditions, exudative and atrophic AMD. In Japan, exudative AMD has been reported at a higher frequency.**

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.

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.



*Age-related macular degeneration

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

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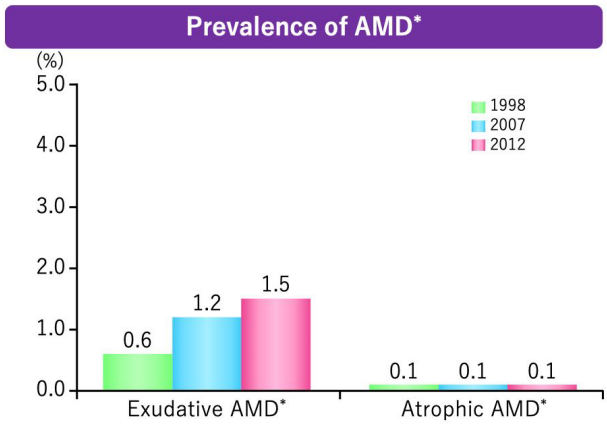
There are two types of age-related macular degeneration, which is also called AMD. One is the exudative type in which new blood vessels grow, as I mentioned, and the other is the atrophic type.

Anti-VEGF medications, such as this Vabysmo, are medication for this exudative type. Unfortunately, no medication has yet been clinically validated for the atrophic type. However, the progression will be slow. In Japan, exudative age-related macular degeneration is by far the most common condition, as will be shown later.

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)

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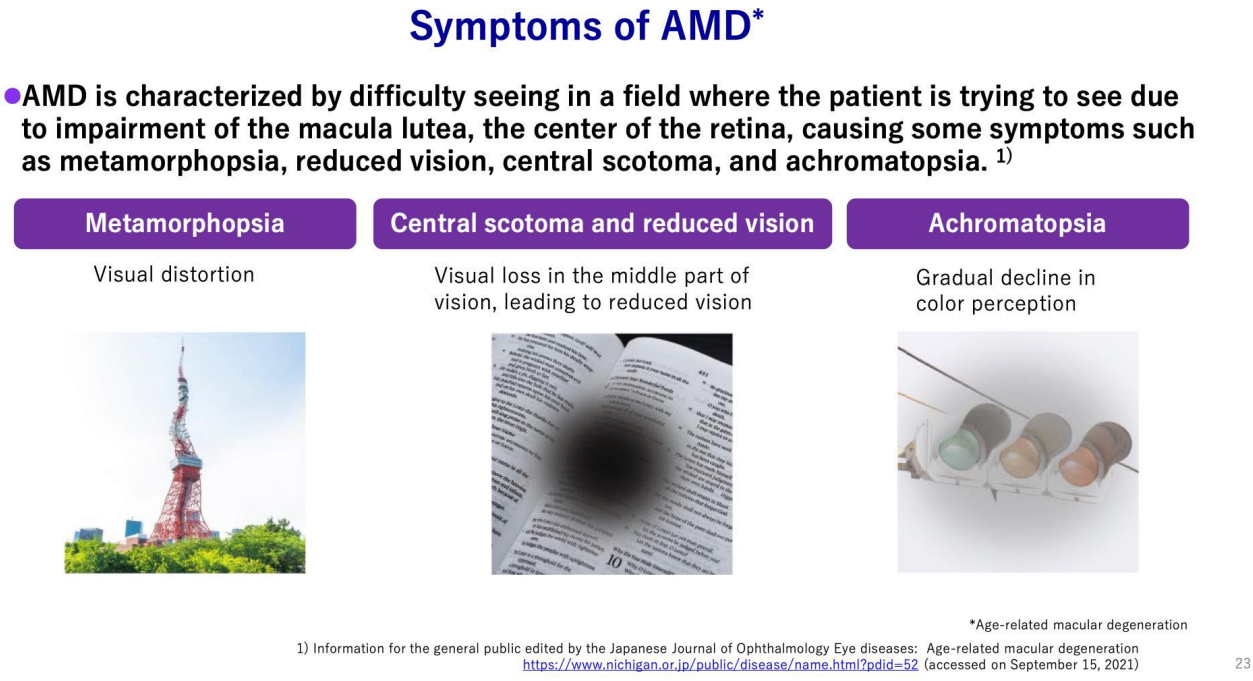
This is the prevalence rate.

These green, blue, and red indicate the prevalence of age-related macular degeneration in 1998, 2007, and 2012, respectively. The left side is the exudative type, and the right side is the atrophic type. As you can see, the atrophic type is very small, 0.1%. As for the exudative type, it was 1.5% as of 2012.

As you can see in this graph, the number of patients with exudative age-related macular degeneration is increasing more and more. In 1998 it was 0.6%, and nine years later it was 1.2%, doubling. If it is increasing further, it is such a disease. Originally, this disease was common in Europe and the United States, but it has been increasing among Japanese and Asians, as shown in this graph.



As I mentioned earlier, this is a disease that causes pathological conditions in the areas where people see and want to see things, so it is a very painful symptom for patients with this disease to lose the ability to see what they are trying to see.

As shown on the left, there are also symptoms such as a distorted appearance of objects, a central dark spot where the center of the eye is dark and cannot be seen, decreased visual acuity, and loss of color perception because the macula contains cells that distinguish colors.

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*

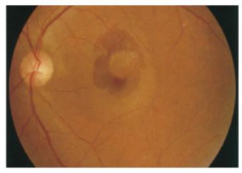
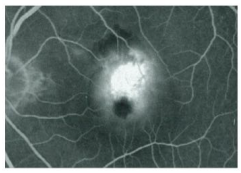
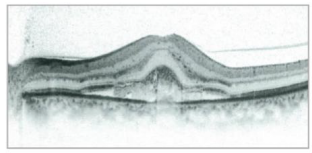


Image of AMD* by fluorescein angiography



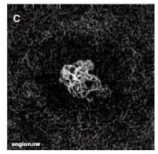
Yamamoto. A. Journal of the Eye. 2018;35 (extra edition):16-20.

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

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About the diagnosis.

In general, the condition of the retina is diagnosed by interview, visual acuity test, fundus examination, and a further test called optical coherence tomography. As for the fundus, as you can see here, color, you can see the hemorrhage here. In the test called fluorescence fundus contrast, neovascular vessels, as the name implies, are newly formed blood vessels, so they are fragile, unlike blood vessels that are already there. So, you can see the contrast agent leaking from there. This allows detection of neovascularization.

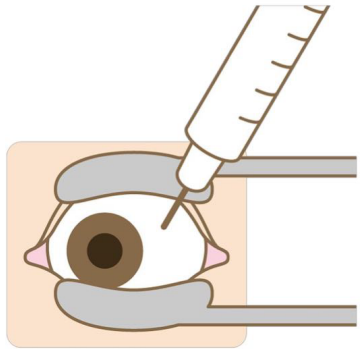
Now, in clinical ophthalmology, this test called optical coherence tomography, or OCT, is becoming very useful, and the widespread use of this test has made it easier to detect patients with age-related macular degeneration, especially exudative age-related macular degeneration. There is also a more advanced method of testing for neovascularization. These tests are used to make a diagnosis of age-related macular degeneration.

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

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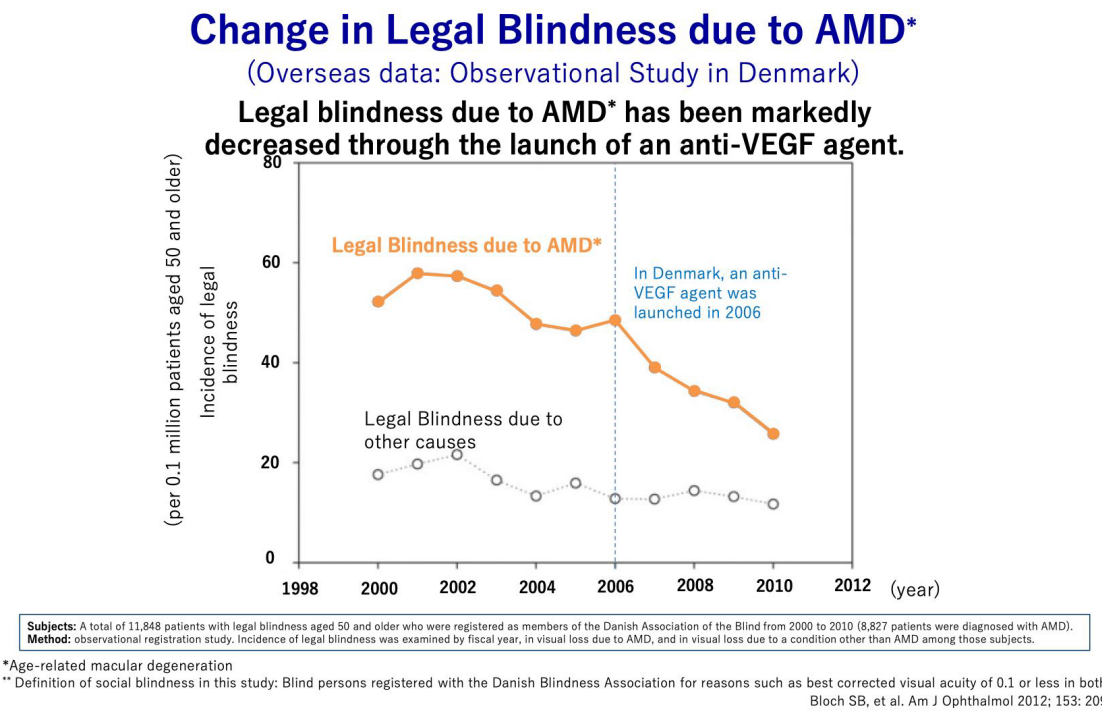
Let's move onto treatment.

Treatments include injections of solutions into the eye, photodynamic therapy, which uses drug and a laser, and laser photocoagulation, which uses a laser to burn down the new blood vessels.

However, the first choice in Japan and the world today is the injection of this drug into the eye, which is the anti-VEGF drug. As Mr. Kishida mentioned earlier, the treatment consists of intraocular injections of drug that suppresses VEGF. The anti-VEGF treatment suppresses the growth of new blood vessels, leakage of blood components, and edema caused by inflammation.

However, although this medication can suppress the neovascular condition, it cannot eliminate neovascular vessels once they have grown. It will remain. Depending on the patient's condition, continuous treatment is required, and this is the disease that needs to be treated. The interval between doses, which will come up a little later, and in continuing to administer, we want to do it as few times as possible.



This is the result of a study in Denmark.

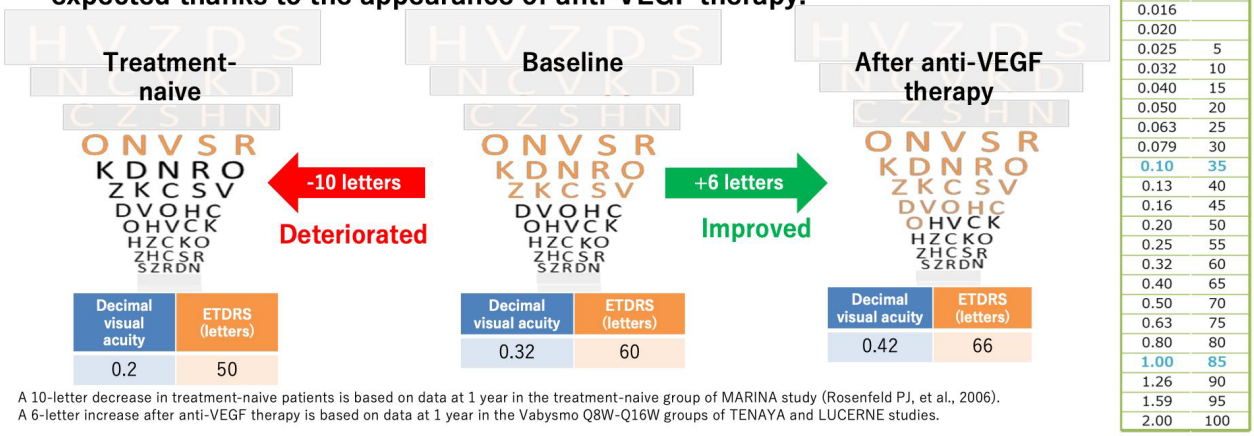
Social blindness is defined as a visual acuity of 0.1 or less, and the graph shows how this has changed over the years. Below this is the number of social blindness per 100,000 people for many diseases. Above this is the number of patients with social blindness due to age-related macular degeneration or AMD. It is the year 2006 that we would like to draw your attention to here. Since then, the number of patients with social blindness due to age-related macular degeneration has rapidly decreased. The number of patients has decreased from about 50 in 2000 to half by 2010. Here, the anti-VEGF medications I mentioned earlier have been launched.

So, this study simply shows that the number of patients with blindness has been greatly reduced by the intravitreal injection of this anti-VEGF treatments.

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.**



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

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I will talk about clinical trials later, but I would like to talk a little bit about visual acuity measurements.

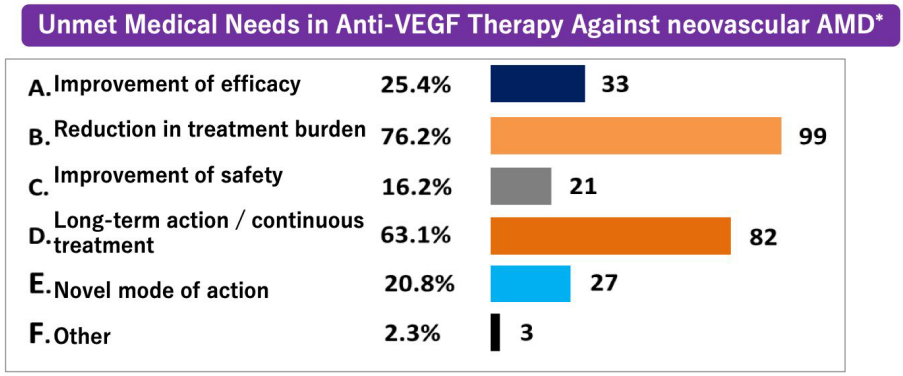
In Japan, we measure visual acuity using Landolt ring and test the vision based on which direction the ring is facing. There is further indication expressed in decimals like 1.0, 0.3, or 0.1. I will briefly discuss the ETDRS chart, an acuity chart used internationally in clinical trials.

You can see that the letters are lighter in color at the top and bottom. This is a method of measuring visual acuity that evaluates how many letters a subject can read. For example, starting from the largest letter on the top, if the total number of letters you identified is 60, then, your score is 60. This 60 is the baseline visual acuity of patients who joined clinical trials for age-related macular degeneration and diabetic macular edema. This equates to 0.3 of normal eyesight level.

What happens to these 60 letters when the disease is left untreated? Past studies have shown that on average, vision is reduced by 10 letters. That would be 50 letters, or 0.2 eyesight. On the other hand, treatment improves visual acuity by six letters, meaning that the number of recognizable letters has increased from 60 to 66 as a result of the treatment.

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.**



[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) 28

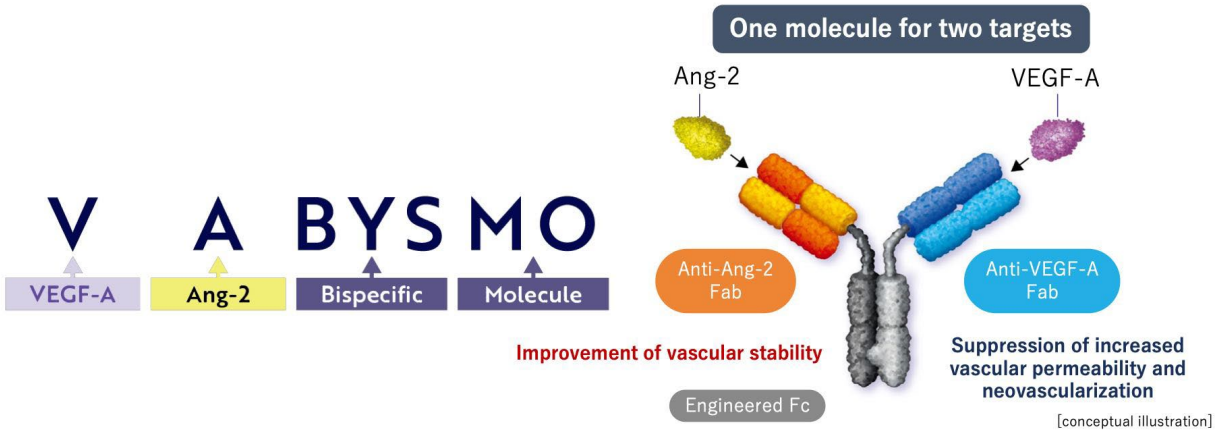
Currently, anti-VEGF therapy is the first choice, and this is a survey about unmet medical needs.

As you can see here, the second is the reduction of treatment burden, and long acting and sustained administration, which you can see is by far the most common. In addition, new mechanisms have been introduced to improve efficacy and safety.

This reduction in treatment burden and long-term effects are closely related to each other. Long-term effects can be thought of as a reduction in the cost of treatment or hospital visits for a patient for a given medication.

Vabysmo

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



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

- Decrease in systemic exposure
- Reduction in proinflammatory effect

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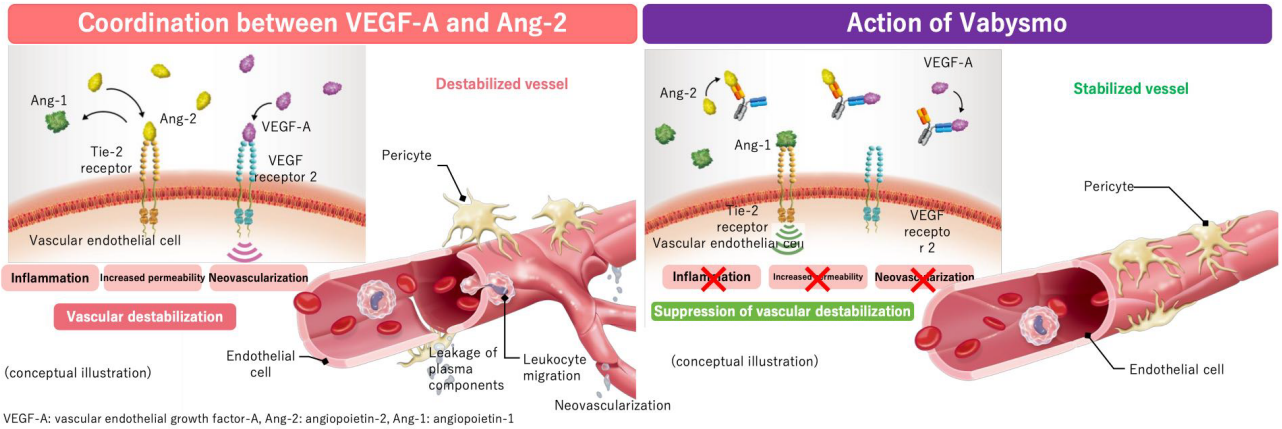
This newly launched Vabysmo has become available for use in clinical settings. As mentioned earlier, this medication not only inhibits conventional VEGF, but also inhibits Angiopoietin-2 or Ang-2 at the same time, thereby stabilizing blood vessels, increasing their permeability, and inhibiting neovascularization.

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.**



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.

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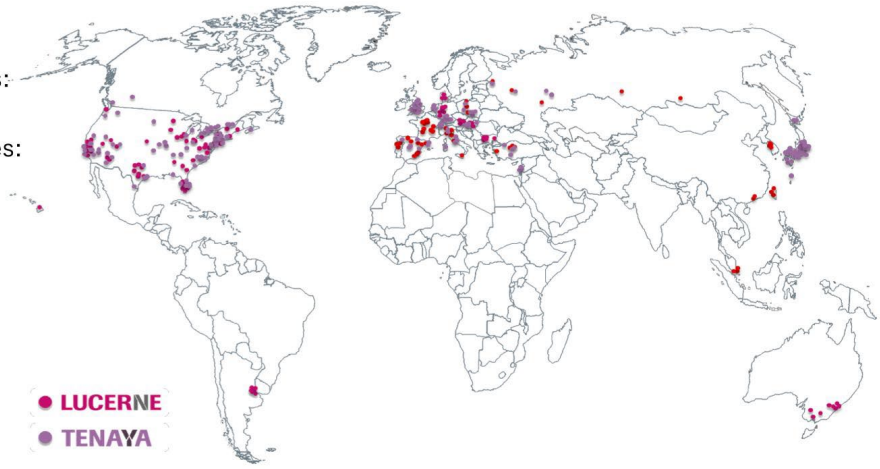
As this is also something that was mentioned earlier, Vabysmo can suppress VEGF and Ang-2 and improve morbidity, which leads to efficacy.

Neovascular age-related macular degeneration

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

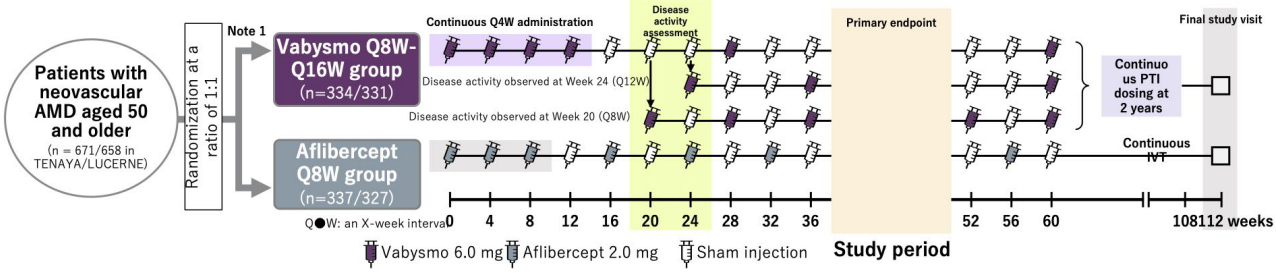
Phase III clinical trials on age-related macular degeneration include the TENAYA and LUCERNE trials. A total of 1,329 patients were enrolled. We in Japan are participating in the TENAYA study.

Neovascular age-related macular degeneration

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.

Here is an overview of the trials. First, the patients are randomized at the stage of enrollment into two major groups: the Aflibercept group, which is conventionally and mainly used clinically, and then the Vabysmo group. Aflibercept is designed to be administered every eight weeks after three intravitreal doses every four weeks, as shown in the attached document.

On the other hand, Vabysmo is initially administered to the patient four times, every four weeks. Eight weeks later, or week 20, the patient's condition must be evaluated. If the condition is stable, observation period begins. If further dosing is deemed necessary, inoculation is resumed at this stage.

Another evaluation be made at the 24-week stage, and patients who require dosing are dosed at 12-week intervals. And even patients without disease activity are administered at this 28-week stage, which is a 16-week interval. The study was conducted at 16-week, 12-week, and 8-week intervals, with three administration courses, and the primary endpoint was how well the patients' visual acuity performed at 40, 44, and 48 weeks.

Neovascular age-related macular degeneration

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.

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Here are the endpoints, efficacy, and safety. We will discuss the results shown in bold blue in the following section.

Neovascular age-related macular degeneration

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

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.

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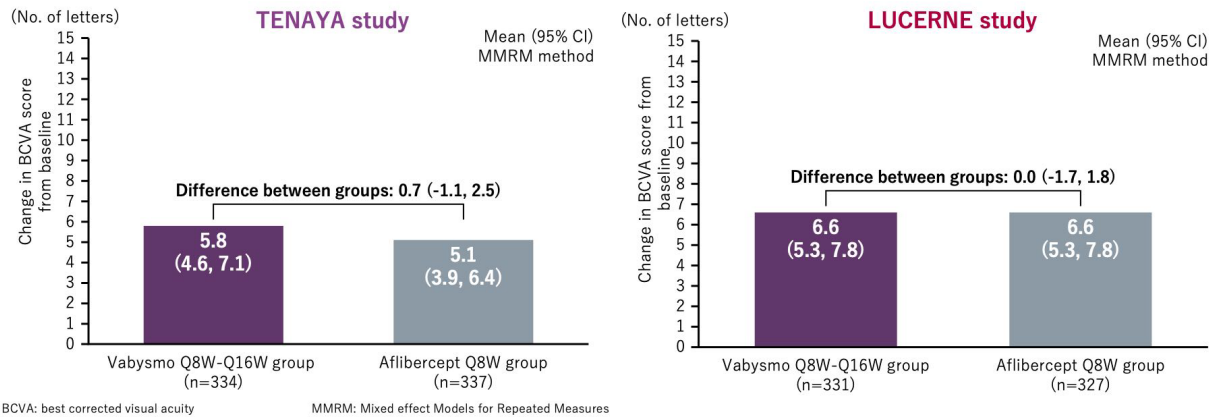
First, the patient's background. As mentioned earlier, the average acuity is about 60 letters at the enrollment stage. This does not differ in any of the groups. So, the primary endpoint is how much this improves or reduces or suppresses visual acuity. There is no difference between the Vabysmo group and the Aflibercept group in both TENAYA study and LUCERNE study.

Neovascular age-related macular degeneration

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

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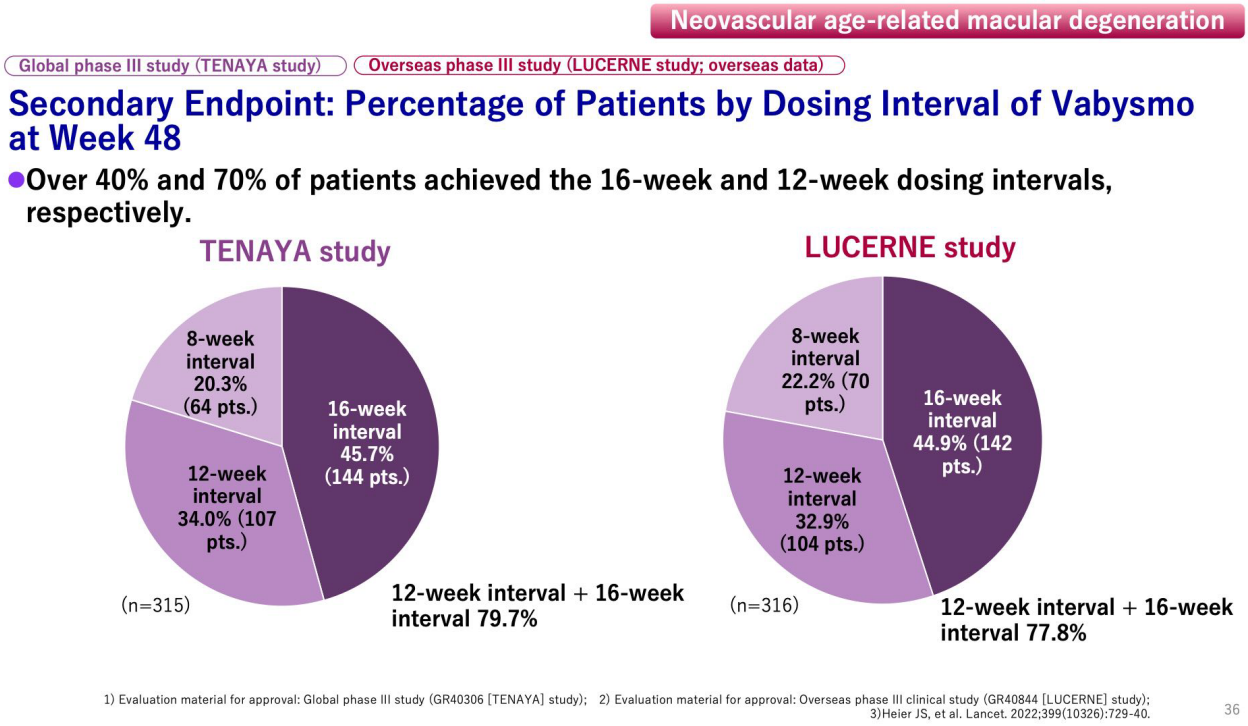
The primary endpoint, the degree of change in visual acuity, is an improvement of approximately six letters in both groups. Therefore, the non-inferiority of the Vabysmo group to this Aflibercept group given every eight weeks was validated here.

The result here is that there is no difference, but as I mentioned earlier, with regard to Vabysmo, there are patients with dosing intervals of 8, 12, and 16 weeks. The total number of patients was found to be non-inferior to Aflibercept every eight weeks.



Let's look for a moment at how many patient groups achieved to 8, 12, and 16 weeks, and here are the results.

Roughly, in the TENAYA trial and the LUCERNE trial, about the same ratio of patients were in the same treatment group as Aflibercept every eight weeks, 20%. Twelve weeks accounts for more than 30%. Just slightly over 30%. Then, the longest dosing interval is 16 weeks, which is around 45% of patients.

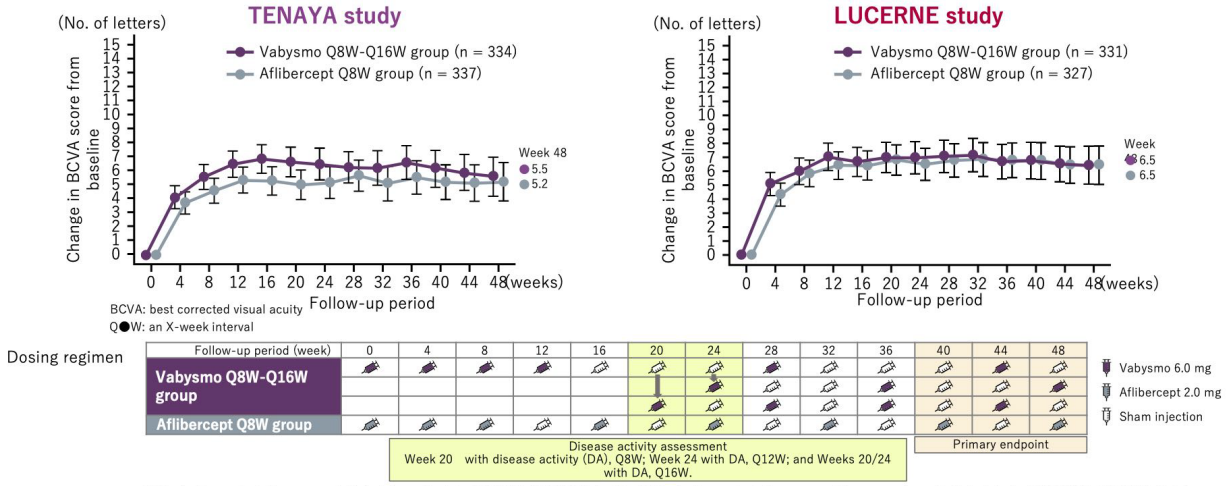
As a result, about 80% of these 12 and 16 weeks combined, including those patients, were non-inferior in acuity.

Neovascular age-related macular degeneration

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.



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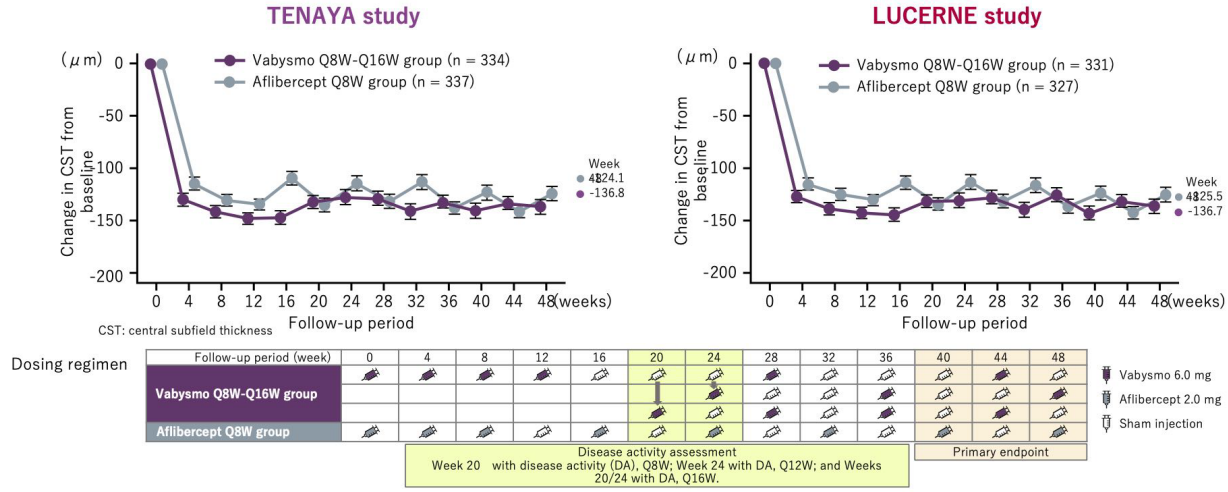
This is a secondary endpoint and is a graph of how much the average change from baseline was. This purple is Vabysmo, and gray is Aflibercept, but there was no difference between the two groups in both studies.

Neovascular age-related macular degeneration

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



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This one is looking at the retinal thickness, the thickness of the retina, and that of the central part of the retina. You have edema at the macula, which causes thickening of the retina, more so than normal. That is why this graph shows the extent to which treatment improves the thickened retina.

If you do, you will see a rapid improvement in retinal thickening after one dosing compared to pre-treatment. Subsequent dosing has helped to maintain that status. This also did not differ between the Aflibercept and Vabysmo groups.

Neovascular age-related macular degeneration

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.

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Next, we move on to side effects.

As this is a medication administered directly into the eye, so side effects to the eye must be taken very carefully. As I briefly mentioned earlier, retinal pigment epithelial tear, uveitis, this is inflammation. There are some of those side effects.

However, there is no difference between Vabysmo and Aflibercept, and there was no difference in Japanese patients. I will discuss this inflammation a little later.

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.

Side effects other than ocular side effects, which are injected into the closed cavity the eyeball, are also something to be aware of, especially since the drug suppresses VEGF, and how it affects the whole body. There is no difference in cardiovascular side effects, which have been known for some time, and no new ones have been reported.

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).**

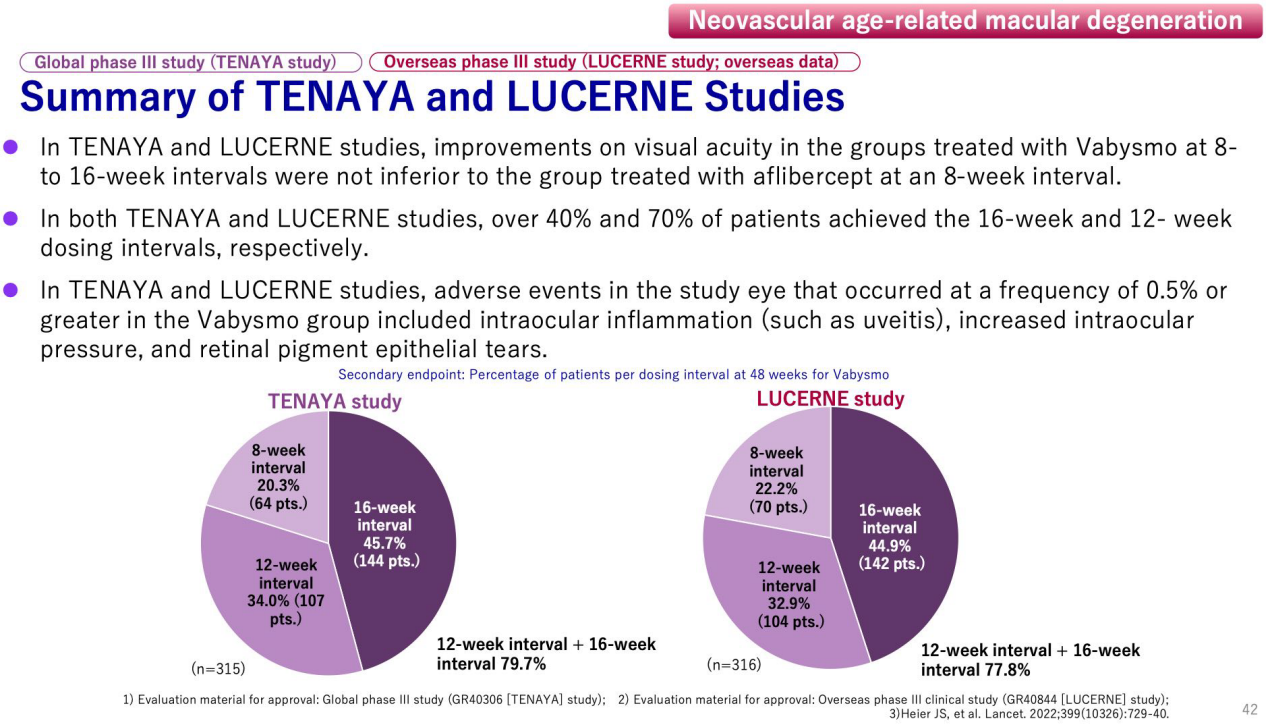
		TENAYA study		LUCERNE study		Overall nAMD	
		Vabysmo Q8W-Q16W group (n=373)	Aflibercept Q8W group (n=377)	Vabysmo Q8W-Q16W group (n=331)	Aflibercept Q8W group (n=326)	Vabysmo Q8W-Q16W group (n=704)	Aflibercept Q8W group (n=703)
Adverse Reactions		5 (1.3)	2 (0.5)	5(1.5)	6 (1.8)	10 (1.4)	8 (1.1)
Serious 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.

This is intraocular inflammation, and this is the table that discusses it. There have been a few cases with Vabysmo, and then some cases with Aflibercept. Here is the combined TENAYA/LUCERNE study, but there was no difference between Vabysmo and Aflibercept.

Then there is also the severity level here, which can be mild, moderate, or severe. The results show that many of these patients are recovering in the trial. Intraocular inflammation was a concern and a problem with some anti-VEGF medications, but in this Vabysmo, the frequency was very low in clinical trials. It also showed no difference from aflibercept.



This will be a summary in the Age-Related Macular Degeneration and TENAYA/LUCERNE studies.

In both studies, 8-week to 16-week intervals of Vabysmo showed non-inferiority of visual acuity improvement to the Aflibercept 8-week interval group.

We were able to achieve 16-week intervals in more than 40% of those patients, and then 12-week or longer intervals in more than 70% of those patients.

Adverse events in the study eyes that occurred at a frequency of 0.5% or greater included intraocular inflammation, increased intraocular pressure, and retinal pigment epithelial tear.

The second point, that the medication could be administered at 12-week or 16-week intervals, is that it is expected to reduce the burden on patients during long-term administration, as mentioned earlier in the section on unmet medical needs.

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

Diabetic Macular Edema (DME)

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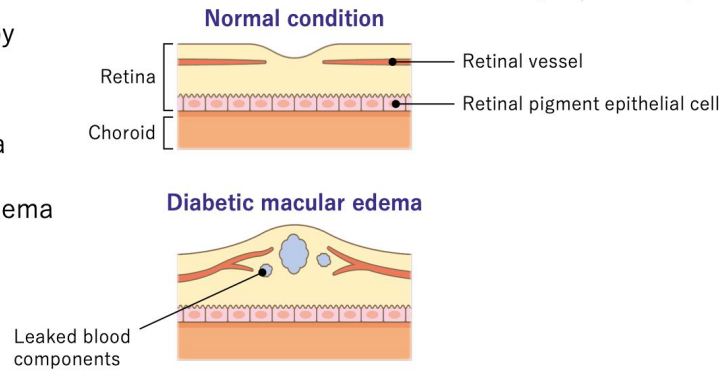
Next is diabetic macular edema. This is a disease in which the blood vessels of the retina are damaged by diabetes, causing edema in the macula, which in turn causes vision loss.

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

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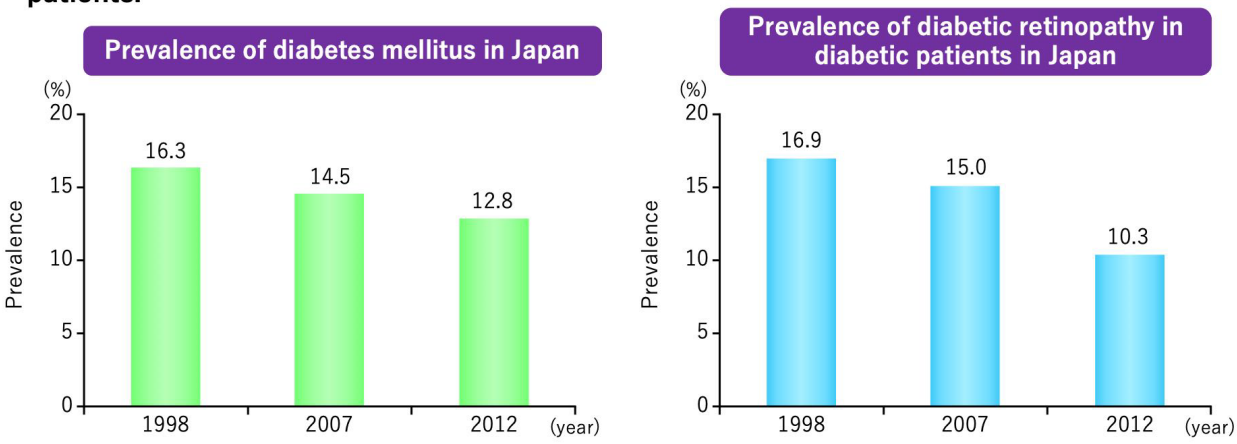
In diabetic retinopathy, the blood vessels in the retina are damaged. This causes exudation, or water leakage and edema, especially in the macular area, or the center of vision, which is called diabetic macular edema or DME.

Prevalence of Diabetes Mellitus and Diabetic Retinopathy

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



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.

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So, what about the prevalence of diabetes and diabetic retinopathy?

In Japan, the prevalence of diabetes and retinopathy is gradually decreasing year by year.

This decrease in the prevalence of diabetic retinopathy is also largely due to advances in overall diabetes and diabetic medical therapy. However, regarding diabetic retinopathy, this is one of the major causes of visual impairment in Japan.

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)

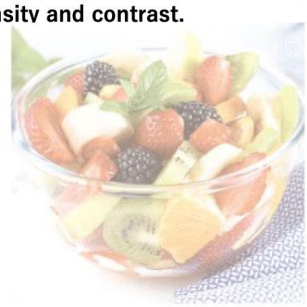
This is the most recent data available, 2015.

Glaucoma is in first place, followed by retinitis pigmentosa, a congenital disease where there is currently no cure. In third place is diabetic retinopathy. In the past, diabetic retinopathy ranked first. There was a time when that was the case, but advances in treatment have gradually brought that down the pecking order, which is a very good thing. In addition, macular degeneration, including age-related macular degeneration, which I mentioned earlier, is positioned in fourth place.

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.



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)

*DME: diabetic macular edema

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This diabetic macular edema, DME, and its symptoms are also similar to those of age-related macular degeneration. The macula is affected, so it appears distorted, and the center of the image appears blurred. The disease is also characterized by the lack of clarity in color shades, light and dark, and the appearance of such.

Moreover, diabetes is a systemic disease, so when these symptoms occur in both eyes equally, this is one of the characteristics of diabetic macular edema.

Examinations and Diagnosis of DME*

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

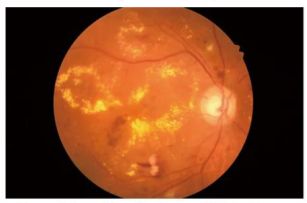
Funduscopy

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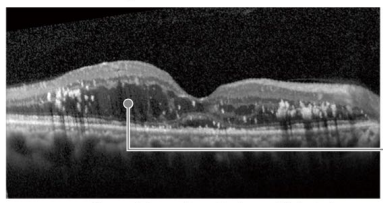
A cross-sectional image of the retina with DME* by OCT**



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

*DME: diabetic macular edema **OCT: optical coherence tomography

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

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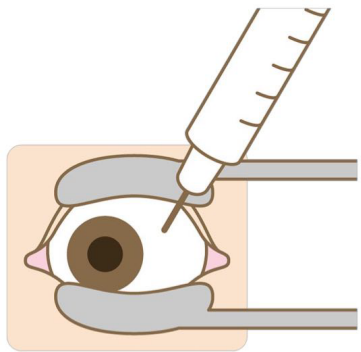
As for the examination, it is the same as for age-related macular degeneration mentioned earlier. This optical coherence tomography is a test that looks at a cross-section of the retina, and the black area, where water accumulates, is swollen, which is the finding of edema.

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

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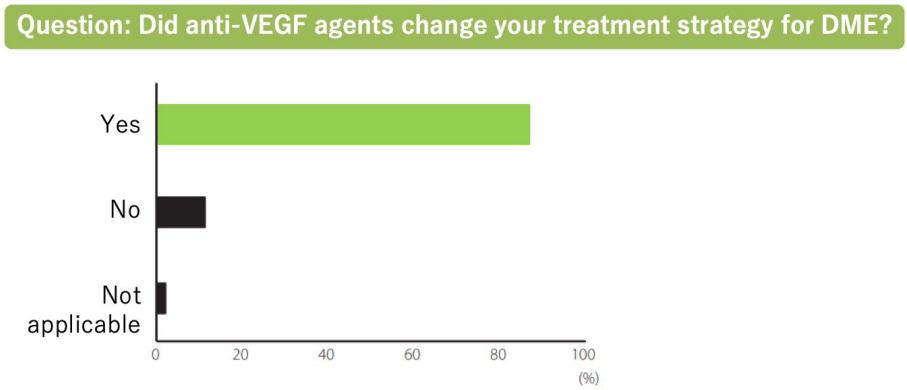
It is a treatment for diabetic macular edema. The basic principle is still blood sugar control and medical treatment. Retinopathy is treated in the stage of macular edema by injecting drugs into the local eye, including anti-VEGF drugs and sometimes steroids. Laser photocoagulation and vitreous surgery are also available, but the first choice at present is the intravitreal injection of anti-VEGF drugs. This will reduce macular edema by

suppressing VEGF, or some sort. The same will be true for this diabetic macular edema, which requires continuous treatment.

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

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



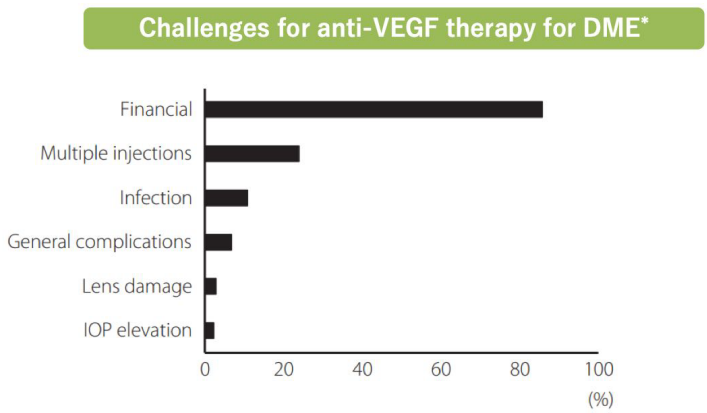
Subjects and methods: 176 physicians treating DME in Japan were surveyed (multiple choices allowed).
Questionnaire method: Questionnaires were sent to consenting ophthalmologists from March 2016 to June 2017, and the responses obtained were tabulated.
*DME: diabetic macular edema

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

The question is what impact the introduction of this anti-VEGF medication had on DME. When we asked the retina specialists if they had made any changes in their treatment strategies, about 90% said yes. It is this anti-VEGF medication that has changed the treatment of diabetic macular edema so dramatically.

Challenges for Treatment of DME* in Clinical Settings

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



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.

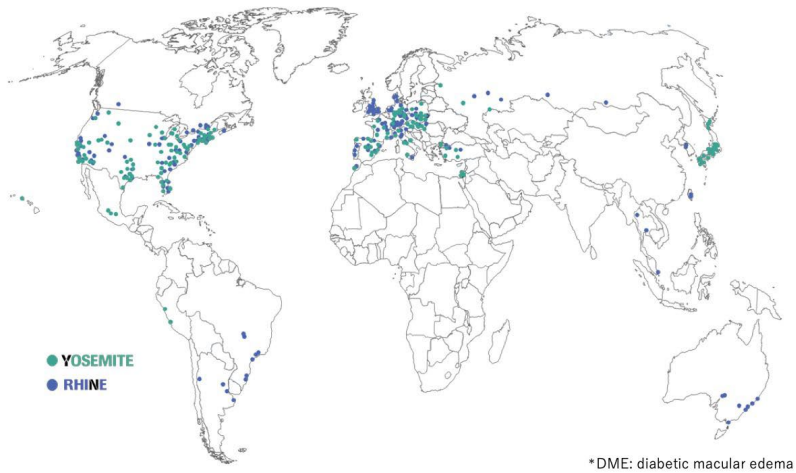
Looking at the challenges of diabetic macular edema treatment in actual practice, the overwhelming majority, nearly 90%, cited financial burden. Since continuous treatment is necessary, the cost of treatment and the

high cost of the medications are a major issue for patients. Related to this, the burden of frequent injections is not only financial, but also the burden of hospital visits.

Diabetic macular edema

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.

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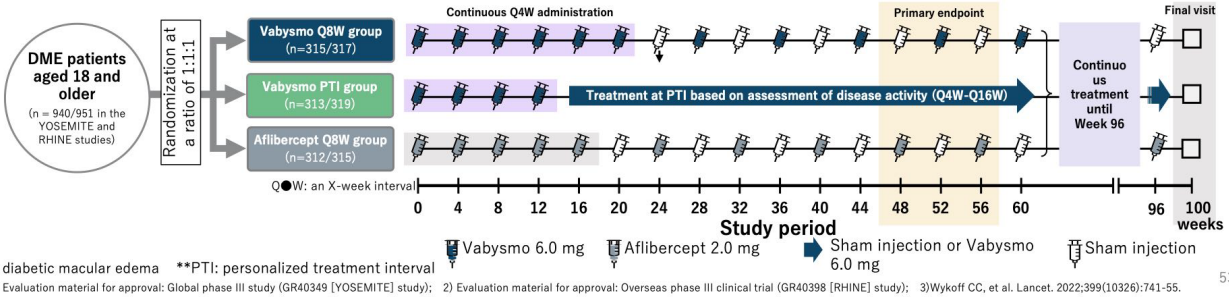
Two trials, YOSEMITE and RHINE, were conducted for macular edema in this Vabysmo, and 1,891 patients were enrolled worldwide. Japan is in the YOSEMITE test.

Diabetic macular edema

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.

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Here is a summary of the test on this.

What is different from the age-related macular degeneration described earlier is that patients are first divided into three groups. As for Aflibercept, this is also as per the package insert, but in the form of five injections every four weeks initially and then every eight weeks.

As for this Vabysmo, it is injected every four weeks for one, two, three, four, five, and six injections. Thereafter, there is one group every eight weeks. The other group consists of three groups of patients who received four injections every four weeks, and then the interval between injections was adjusted according to the state of the disease, which I will not show today because it is a rather complicated standard.

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

Diabetic macular edema

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

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.

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As expected, the primary endpoint will be the change in visual acuity. We will look at the effectiveness and safety of this bold indication later.

Diabetic macular edema

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

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.

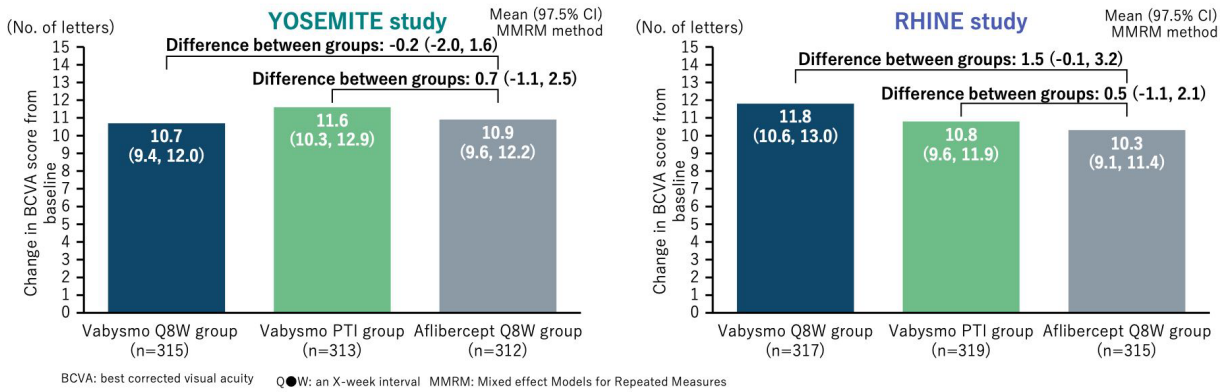
First, the patient's background. As you can see here, we would still have seen that the pre-treatment visual acuity was about 60 letters, and again, there was no difference between any of the groups. There is no difference among the Japanese.

Diabetic macular edema

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.**

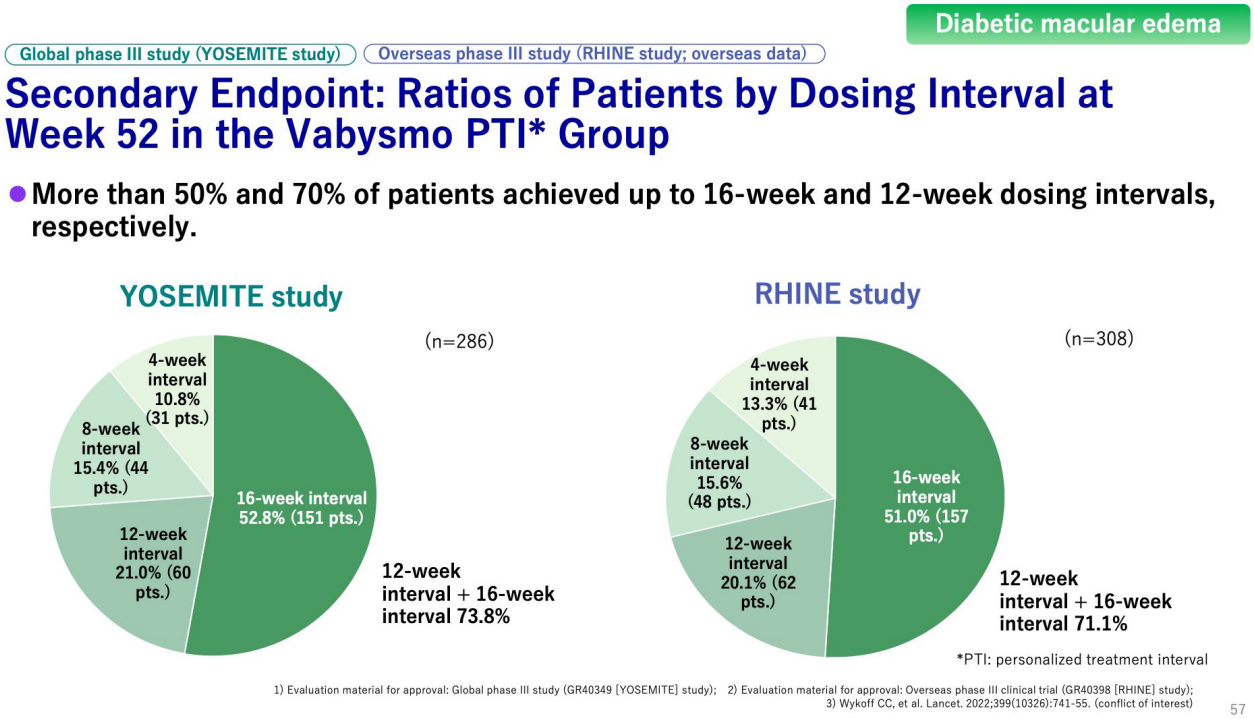


BCVA: best corrected visual acuity Q●W: an X-week interval MMRM: Mixed effect Models for Repeated Measures

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.

Here are the results of the primary endpoints. As you can see here, there is no difference between the group that received Vabysmo every eight weeks, then the group that received it depending on the condition, then the group that received Eylea Aflibercept every eight weeks. So, the non-inferiority of Aflibercept to the 8-week group was proven. This is the same for both the YOSEMITE and RHINE exams.

Non-inferiority was proven, but what about the group that I mentioned earlier, which is right in the middle here, where the dosing interval can be adjusted, and the dosing interval is adjusted according to the patient's condition?



In this graph, the trend is very similar, but first about 10% were administered at four-week intervals, then about 15% at eight-week intervals, and 21% at 12-week intervals, which is more than half of the patients who had achieved a whopping 16-week interval.

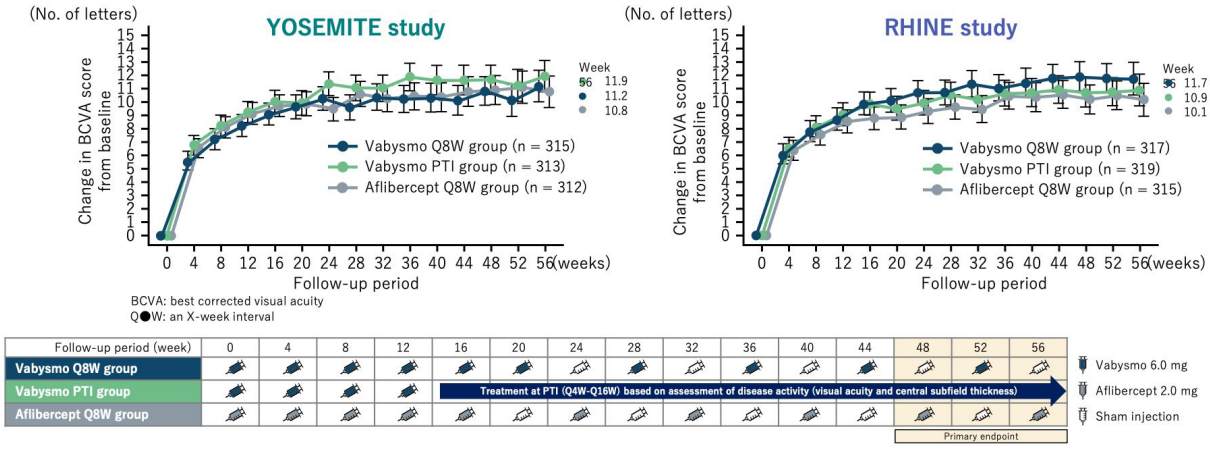
More than 70% of the cases at 12 and 16 weeks combined were patients with this long dosing interval. This is the reason why there was no difference in terms of improvement in vision.

Diabetic macular edema

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.



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.

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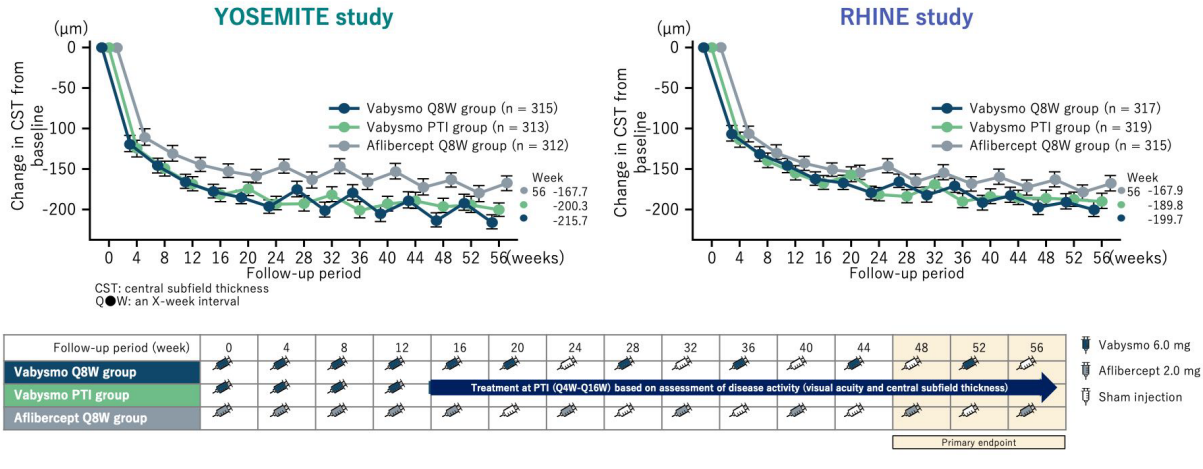
This is the change in visual acuity for those three groups, and the results are almost the same, with no significant differences.

Diabetic macular edema

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)



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.

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This is a change in the thickness of the central retina, but the retina is thickened because of edema. The three groups showed a rapid improvement in thickening after the medication was administered, followed by a gradual improvement, and then maintenance of this improvement. This also makes no difference.

Diabetic macular edema

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	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 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.

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Next, we move on to safety.

First, safety for the eye is a transient increase in intraocular pressure. As mentioned earlier in the case of age-related macular degeneration, the intraocular pressure rises because a small amount of the medication is administered into the closed space eye, and the volume of the eye rises slightly.

There were also some side effects such as vitreous floaters, but these did not differ from the previously known side effects, and I will discuss inflammation in a later session.

Diabetic macular edema

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	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)
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

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

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This is the result of other side effects such as keratitis, uveitis, and so on. No new case has been reported for this either.

Diabetic macular edema

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

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

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Aside from the eye, diabetic patients also have a background of systemic diseases, diabetes, which should be taken into consideration as well as age-related macular degeneration. Again, there is no difference in both groups and in both medications, and no new ones have been observed.

Diabetic macular edema

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.

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. 63

Inflammation within the eye was observed in nine cases in the Vabysmo group and two cases in the Aflibercept group in two studies of diabetic macular edema. There are mild, moderate, and severe symptoms; but as I mentioned earlier with age-related macular degeneration, many patients are recovering from this as well.

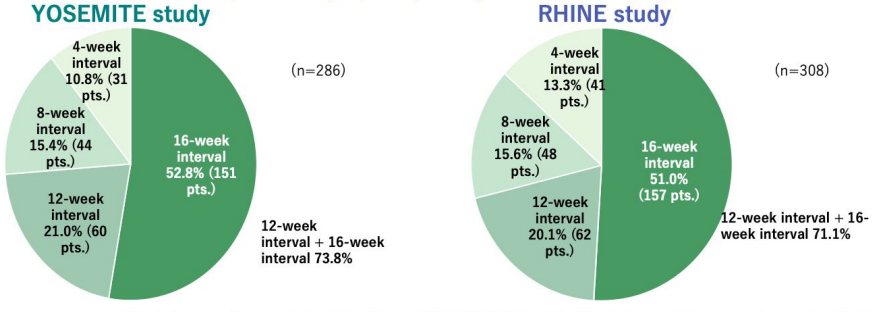
Diabetic macular edema

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



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. 64

This is a summary of both examinations. First, Vabysmo, the PTI group, which is administered up to 16 weeks apart, and is a patient-specific group, showed non-inferiority of visual improvement over the Aflibercept eight-week interval group. Non-inferiority was found, with more than 50% of the patients achieving a 16-week interval and more than 70% achieving a 12-week or longer dosing interval.

Adverse events and side effects observed with a frequency of 0.5% or greater include intraocular inflammation, increased intraocular pressure, and vitreous opacities. This, too, as I mentioned earlier for age-related macular degeneration, again, the fact that we were able to extend the dosing interval in a significant number of patients will be a unique feature of this medication.

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)

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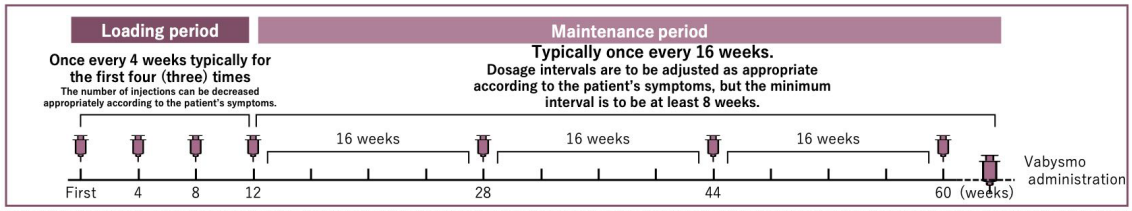
Vabysmo was launched at the end of May and is now being administered in our clinical practice for exudative age-related macular degeneration and diabetic macular edema.

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) 67

This is a duplicate of Mr. Kishida's earlier slide, but I will first show the dosage and key points in red for age-related macular degeneration.

As was mentioned earlier, four consecutive doses, the induction phase, is administered. The frequency of administration should be reduced according to symptoms. So, then the maintenance phase was administered every 16 weeks. However, it is also stated that this can be adjusted, but at least eight weeks apart.

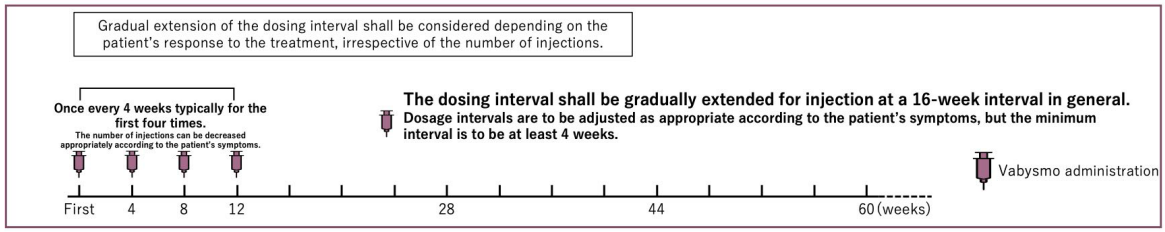
Conventional solutions, anti-VEGF solutions, are usually injected during the induction phase, three times. However, although the dosage is stated as four times with Vabysmo, in the Precautions Related to Dosage and Administration section, it is stated that the induction period should be considered as three consecutive times, which is very user-friendly for us clinicians.

The same applies to the consideration of a dosing interval of 8 weeks or 12 weeks. It is very gratifying to see such an attached document that can be used flexibly depending on the patient's condition.

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.

Digitalized Package Insert of Vabysmo Solution for Intravitreal Injection 120 mg/mL (March 2022; Version 1) 69

As for diabetic macular edema, this was also mentioned earlier, but the point is this. It is administered in the vitreous four times in a row, but the number of doses may be reduced according to symptoms. Usually once every 16 weeks, with a minimum of four weeks between visits. Earlier, for age-related macular degeneration, it was stated to allow at least eight weeks, but for diabetic macular edema, it is stated to allow at least four weeks, as reflected in the design of the clinical trial.

In addition, in the section entitled Related Precautions, there is a section that states that regardless of the number of times the medication is administered, consideration should be given to gradually extending the administration interval in response to treatment response. I am very grateful for the inclusion of this information.

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

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As for side effects, as mentioned earlier, this also overlaps slightly. Eye disorders, stroke, and others are mentioned in the attached document.

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.

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Here is a little summary of what we clinicians can expect from this newly emerged Vabysmo. This new medication suppresses not only conventional VEGF but also Ang-2. With this novel mechanism of action and its therapeutic effect, it is expected to become a treatment option for patients for whom conventional medications that only suppress VEGF have been insufficiently effective. I expect so; I'm even excited.

The other is that in both clinical trials, improvement in visual acuity was achieved even at longer dosing intervals, such as 12 weeks or 16 weeks, which is longer than conventional dosing intervals, and the results showed that the effect was sustained. This will reduce the burden on the patient, not only financially, but also in terms of hospital visits, and in the case of elderly patients with age-related macular degeneration, the burden of accompanying the patient's family members, who often come to the hospital together. We believe that this can be expected to reduce the burden of accompanying family members.

As for side effects, no new ones that differ from the conventional ones were found in the clinical trials, and the number of side effects such as intraocular inflammation, which is something we should be concerned about, was small. The results of the clinical trials are encouraging, but we need to carefully monitor the results in actual clinical practice.

That's all from me. Thank you very much for your kind attention.

Sasai: Thank you very much, Dr. Iida. Please feel free to have a seat.

Question & Answer

Sasai [M]: We will now begin the question and answer session. We sincerely appreciate your cooperation in limiting the number of questions to two per person to encourage more people to ask questions. Please note that the audio file of the Q&A along with the presentation will be posted on our website at a later date.

First, we will take questions from those attending on-site, followed by those attending via Zoom webinar. If you have any questions, please raise your hand. Our staff will hand you a microphone. Please state your affiliation and name, and then ask your questions.

Hashiguchi [Q]: I am Hashiguchi from Daiwa Securities. Thank you very much for your briefing. I have a question for Dr. Iida. The dosing intervals of Aflibercept or Eylea was eight weeks apart in the trials, but I think it can be adjusted in real clinical settings. How many weeks apart is Aflibercept administered in most cases in reality? What do you think about the ease of adjustment? If you can't tell how long or short a medication will work for a patient until you try it, I think it will be very difficult to adjust the medication interval. Do you feel that there is a difference in the ease of adjustment for each medication?

Iida [A]: Thank you. I am impressed, the question shows how well you are informed already. First, as you have just asked, in real clinical settings, we use Eylea while adjusting the dosing interval. The clinical trial of Eylea, called the VIEW trial, was the same as the TENAYA trial, which was conducted every eight weeks after three doses. That's how the approval was granted for this medication.

Therefore, the package insert also states that the dosing interval should be adjusted accordingly. Since this is the case, we extend the administration to those patients for whom we can extend it. The most common clinical practice now is to extend the dosing interval after three doses or shorten it if a recurrence occurs. This is the method used by many retina specialists.

In such dosing intervals, there are about 40% of patients can obtain dosing intervals of 3 months, which is 12 weeks, or 16 weeks. On the other hand, however, some patients cannot extend the dosing interval from every four weeks or every eight weeks, which is about 40% of the patients.

As for Vabysmo, we only have data from clinical trials at the moment. I do not know how it would work in real clinical settings, but the fact that a large percentage of patients were administered at extended dosing intervals of 12 or 16 weeks leads me to the last point I mentioned earlier, that it may be possible to administer the medication at longer dosing intervals. Therefore, we have just started using the medication in the hope that it will help extend the dosing interval. As for its usability, we intend to look at this while accumulating actual clinical results in addition to clinical trial data. Did that answer your question?

Hashiguchi [Q]: Thank you very much. The second question is how would you explain the cost of the medication to the patient? I think the medication cost per dose is higher for Vabysmo. If the duration is extended as per the package insert, I think Vabysmo would be an economical option for the maintenance period, but as you said, the actual dosing interval varies from patient to patient. Some pay more, some pay less. I'm not versed with the high-cost medical care system and how it may be affected. Could you help me with that?

Iida [A]: Thank you. I had extensive discussions with the doctors practicing with us. As you point out, Vabysmo has a higher medication cost compared to conventional agents. I remember that the fee was roughly an additional JPY8,000 if the medical expenses were covered at 30% of the patient's cost. We always explain to the patient that the cost could be in that range for a single administration.

We have just recently incorporated Vabysmo and also started to introduce it as a new option for patients who have had an inadequate response to the conventional approach. We ensure patients understand the cost increase. Patients themselves have high expectations for new medications because they have not had sufficient effect with conventional medications, so they are willing to accept the financial burden.

The other point is, regarding new patients, in other words, patients who are about to start treatment, I would still like to explain to them that when they use this Vabysmo, they can expect the dosing interval to be extended based on clinical trial data, and then what to do when they see the total results. Although it may be slightly complicated for patients to understand, we use it only after they understand the financial burden in the long run. It is in actual clinical practice that the effect of being able to suppress both targets, not only VEGF-A but also Ang-2 is explained at the same time, and the final decision is made as to which medication to use.

Hashiguchi [Q]: What is your thought on the high medical expenses reimbursement system?

Iida [A]: Yes, that is in our scope, and we provide ample information to our patients. This is another highly complicated structure, with annual income restrictions and all that. Therefore, since we doctors are not able to explain ourselves, we ask our administrative staff to provide information to patients.

Hashiguchi [Q]: Should we not think too much about the way that the coverage changes with different dosing intervals, and that the simple difference in medication cost reverses the patient burden?

Iida [A]: I think that may be affected by the high cost of medical care. However, that is not such a big difference. As I am sure you know since you are asking these questions, the price of generic drugs is quite low. I think the relationship will grow in such cases.

Hashiguchi [M]: Thank you.

Sakai [Q]: My name is Sakai from Credit Suisse Securities. Thank you for your presentation today. I'm afraid I'm not an expert on the topic. The clinical trial results indicated non-inferiority in terms of therapeutic efficacy, but provided that the administration period can be extended. I presume you had some expectations about the superiority. How do you evaluate the results? Compared to Aflibercept or Eylea, the treatment results were all the same. Am I correct in understanding that patients and clinicians are somewhat satisfied with the therapeutic effects?

Iida [A]: This is another question from a well-studied perspective. I'm surprised. First, I guess you are asking if I am satisfied with the fact that it was non-inferiority. Yes, I'm fine with the result. This is because the first clinical trials of anti-VEGF medication improved patients' vision very much. Conventionally this disease was thought to be never improved. However, the anti-VEGF medication demonstrated vision improvement with superiority, not non-inferiority. The medication was Lucentis. When using those drugs as comparison groups, there is a limitation in terms of the degree of improvement in vision.

This time, we have six letters, but again, six letters are the current standard of acuity for inclusion in any clinical trial using any medication. This is slightly complicated, but the vision of newly enrolled patients is slightly better than that of the beginning. In the beginning, we had many patients with poor vision, about 0.5. That was the criteria we used at that time. It turned out that we didn't ensure enough headcounts to start. Hence, we bring up the vision threshold for the current clinical trials. While the scope of the increase is very narrow, just because the vision has increased a little, the range of improvement is narrowed, ironically. Sight is like that.

Therefore, I consider these six letters threshold to be equivalent to the highest peak reached by conventional medications. I think that is non-inferiority. Six letters are for age-related macular degeneration. I believe that

10 letters in diabetic macular edema, a certain number, or numbers like that, is the number that will be hit on the head there.

Sakai [Q]: Thank you very much. Also, one more thing, on this chart, and you mentioned earlier that it was like a choice to some extent due to medication prices, but the point is that so much VEGF, and also Lucentis and Eylea, is there going to be some BS soon, or is it already out there.

Iida [A]: Thank you. Lucentis's BS is launched.

Sakai [Q]: It's out there, I think it's Senju or some other company. Anyway, that's true, and with so many options, in a sense, for clinicians, it's unthinkable to put two expensive medications at one facility. For Eylea, the only indications so far are DME and AMD, and the other VEGF medications have more small indications. As you explained this time, I wonder if these differences will be an obstacle to some extent for doctors in their choice, or if there will be more cases of selecting faricimab for DME and AMD, which are the most common diseases, in terms of usability for now. I would like to ask you a few questions about these areas, just in general.

Iida [A]: It is very gratifying for us clinicians to see such an increase in the number of medications. I mean, not all of them work the same for every patient. As I mentioned earlier, there are a certain number of patients who do not respond to treatment with Eylea or Lucentis. In such cases, we switch to different medications. Sometimes it works. We are hoping that this switch, and the fact that Vabysmo is an add-on medication that also suppresses Ang-2, will have a positive effect on Vabysmo.

We have more options, and in the meantime, we have all at the Tokyo Women's Medical University available to us. However, some patients simply do not meet our expectations, depending on their condition, so we use different medications to maintain or improve their vision.

Sakai [M]: Thank you.

Saga [Q]: I am Saga, a freelance writer. Thank you for taking my question. I would like you to continue the topic you have just mentioned. If you expect some VEGF in the first patient, I would like to know where and what kind of medications you use.

Iida [A]: About Eylea, the condition in which Eylea has been used most often up to now is that patients with lesions located in the lower part of the retina, which in the case of age-related macular degeneration is called the retinal pigment epithelium, and the lesions are mainly located below that area, are more likely to benefit from Eylea than Lucentis. We have such data, and we also believe so, and that is why we used Eylea.

Saga [Q]: By the way, what kind of patients do you think would benefit from Lucentis?

Iida [M]: Just age-related macular degeneration and diabetic macular edema?

Saga [M]: Yes, that's right.

Iida [A]: Lucentis works concerning lesions on the retinal side of the retina rather than the retinal pigment epithelium. But here's one problem**:** the dosing interval, actually. The dosing interval for Lucentis started as a monthly dose, and next Eylea was introduced to extend the interval a little. Therefore, the dosing interval tends to be a little shorter when Lucentis is used. We are currently selecting medications while taking this into consideration.

Saga [Q]: Thank you. One more point. Do this VEGF and Ang-2 bispecific effect directly speak to the prolongation of the dosing interval?

Iida [A]: I expect that. In a basic research animal study, in which neovascular vessels were created as a model for age-related macular degeneration and medications were administered to them, the results showed that suppressing Ang-2 together suppressed regression of neovascular vessels and leakage from neovascular vessels better than suppressing VEGF alone. So, I think that suppression of neovascular activity is obtained by suppressing Ang-2 together. If so, I would expect that the water leakage would be controlled, and the interval of dosing would be prolonged during that time. One-time dosing effect and then the interval, that's what I'm hoping for.

Saga [M]: I understand. Thank you very much.

Sasai [M]: I would like to continue by taking questions from those who are joining us online. I would like to introduce the first question. Mr. Yamaguchi of Citigroup Securities, please go on.

Yamaguchi [Q]: My name is Yamaguchi. Thank you very much for this opportunity. My first question is about the difference in actual administration. It seems that both solutions are taken from a vial and injected into the eye. Is there any difference in the actual administration of the medications, including the complexity and pain involved in the process, whether for the patient, the nurse who prepares the injection for the doctor, or the doctor?

Iida [A]: Thank you. This Vabysmo will be a medication that is taken from a vial and administered. Eylea, Lucentis, Lucentis BS, and others are a solution that is already in a syringe and pre-filled. Therefore, this Vabysmo is one step added in terms of preparation for administration. They have to suck from the vial. However, I am told that in the future it is scheduled to be pre-filled already.

Yamaguchi [Q]: Thank you very much. Is there any or little difference between the products in terms of the experience of patients who are administered?

Iida [A]: No. We use anesthesia and inject with a thin needle. It's not a painful experience for the patients.

Yamaguchi [Q]: I understand. Thank you very much for this opportunity. One more point, I think you mentioned that you would first use it on people who don't respond well to existing Eylea. It is a little difficult to say how much, but can you tell us that?

Iida [A]: Thank you. Of course, the Phase III clinical trial data are from patients who are about to start treatment, and the data show that the dosing interval can be extended with it, so the medication should be firstly used to those new patients. However, in actual clinical practice, the number of patients who do not receive the full benefit of the treatment is becoming a burden for us physicians as well. I was very distressed because the treatment was really expensive, but it was not giving enough effect.

However, we do not have any data on how effective the new medication will be for patients who did not respond to the conventional medication, but we have to consider that Vabysmo has different mechanisms of action and other factors. So, the patients are fully convinced, or rather, they hope for a change in the medication. Therefore, we are currently administering the medication to patients with inadequate efficacy and new patients.

As to the extent to which the Eylea is not effective, this still varies slightly from study to study. However, it is also a very difficult question as to where to base the criteria for ineffectiveness, but as of two-year treatment , our data shows that about 20% of patients need to be treated at four-week intervals. When it comes to the eight-week interval, it is another 20%, and that is about 40% of the eight-week interval in other studies, so I think that is the figure in actual clinical practice for Japanese.

Yamaguchi [M]: Thank you.

Sasai [M]: Thank you very much.

Muraoka [Q]: Hello. My name is Muraoka from Morgan Stanley. Thank you for taking my question. I too would like to learn from Dr. Iida. I think Vabysmo is a wonderful medication this time in the treatment of this AMD and DME, but what are the next big breakthroughs that you are looking forward to? For example, to my limited knowledge, I believe some companies have taken the approach of making small molecule VEGFR medications into eye drops. I don't mean to dwell on that, but what is the next breakthrough you are looking forward to?

Iida [A]: Thank you. As you have just mentioned, we still expect the administration route to be simple. The simplicity of the route of administration is a big advantage, as injections are not very pleasant for patients, and they have to come to the hospital. I think it will be in terms of effectiveness, weighing how the simplified route of administration will not diminish the effectiveness of the product. As for the route of administration, I think this is one breakthrough.

Another thing we are also looking forward to is a drug delivery system that will have a long-lasting effect. Then there is neuroprotection. Once again, whether it is age-related macular degeneration or diabetic macular edema, other retinal diseases are a matter of how damaged the photoreceptor cells that sense light are. One of the reasons I mentioned that once the damage is done, there is a limit to the improvement in vision because such cellular damage has already occurred, so there is a ceiling. Therefore, I would like to see neuroprotective medications that can reactivate cells that have been damaged by neuroprotection, and I would like to see medications that are effective in this regard. Did that answer your question?

Muraoka [Q]: Thank you. I think the sustained drug delivery, the port delivery of Lucentis, which I think Chugai is doing now, I think it was once every six months, but the doctor said earlier that Lucentis only works on the upper lesions, the corneal epithelium, I think it was. I was wondering about this as I was listening to you. If you could add comments, I would appreciate it.

Iida [A]: Thank you. It is not that it is ineffective, but rather that the effect can be interpreted as being inferior to other medications, such as Vabysmo and Eylea, for the subretinal pigment epithelium with Lucentis. It's not that it doesn't work at all. So, I believe that long-term suppression of VEGF may also affect many lesions below the retinal pigment epithelium. Did that answer your question?

Muraoka [M]: I understand. That's all from me. Thank you very much for this opportunity.

Sasai [M]: Thank you very much. The next question is from Ms. Sato.

Sato [Q]: My name is Sato from Schroder. Thank you for taking my question. I would like to ask you about the case of an existing patient who is switching from another medication to Vabysmo, not a new patient. As stated in the dosage and administration of Vabysmo, is this induction process required even if switching from another medication, i.e., the first time, four cycles multiplied once every four weeks?

Iida [A]: It was a very sophisticated question, and I felt as if I were being asked by an ophthalmologist right now. In fact, in our clinical practice, we have a certain number of patients who receive the medication every four weeks, but there are some patients will longer intervals between doses. For those patients, we do not do it from the initial induction phase. If the interval is stable to some extent with conventional medications, say six or eight weeks, we would feel bad about shortening it with Vabysmo, so we will start by maintaining the interval at six or eight weeks, and see if we can extend it or not. I am now wondering if it is possible to extend the interval.

As for patients every four weeks, when they switch to Vabysmo, they are still scheduled to come in for injections in four weeks. But if we can extend it there, it will be in a form that is not in the introductory phase. Some patients are administered every four weeks and manage to control the progression of their disease in

four weeks, and some patients still have exudation even after four weeks, and there are both. Therefore, the administration interval will be determined based on the state of exudation.

Sato [Q]: Thank you very much. Then, the problem of high financial burden due to the higher cost compared to other medications and the difficulty in explaining this is a problem that applies to a rather small percentage of patients, is it not?

Iida [A]: Although it has only recently been launched and we have only recently started using it, patients for whom conventional medications were not sufficient are still those who have been waiting for a new medication to come out. So, of course, we would tell them the price of this medication and that there is a difference in this amount, but there was no one who did not like it. They all switched to Vabysmo.

Sato [M]: I understand very well. Thank you for taking my question.

Sasai [M]: Thank you. Due to time constraints, we are going to wrap up the Vabysmo presentation. I would apologize to those who didn't have a chance to ask a question today. Please feel welcome to contact our Media Relations and Investor Relations groups. Contact information can be found at the end of the presentation materials. Thank you for taking time out of your busy schedule to join us today.

[END]

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