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Chugai Obtains Regulatory Approval for Vabysmo, the First Bispecific Antibody in Ophthalmology, for Neovascular Age-related Macular Degeneration and Diabetic Macular Edema

- Vabysmo, the first bispecific antibody in ophthalmology, has been approved for neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME)
- The bispecific antibody inhibits two disease pathways that drive nAMD and DME by blocking angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A)
- Vabysmo achieved a maximum 16-week dosing interval for the first time, as an intravitreal injection, in phase III clinical trials for nAMD and DME

TOKYO, March 28, 2022 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced that it has obtained regulatory approval today from the Ministry of Health, Labour and Welfare (MHLW) for Vabysmo® for Intravitreal Injection 120 mg/ mL (generic name: faricimab) (hereafter, Vabysmo), an anti VEGF/anti Ang-2 bispecific antibody for the treatment of "age-related macular degeneration associated with subfoveal choroidal neovascularization" and "diabetic macular edema (DME)." Age-related macular degeneration associated with subfoveal choroidal neovascularization is generally known as neovascular age-related macular degeneration (nAMD).

"Vabysmo is the first bispecific antibody in ophthalmology. We are very pleased that a new therapy based on a novel mechanism of action has been approved for two diseases that may potentially lead to vision loss," said Chugai's President and CEO, Dr. Osamu Okuda. "This marks a full-scale entry into the ophthalmology field for Chugai. Vabysmo is expected to improve vision loss and reduce treatment burden by potentially offering 16-week dosing interval. We are preparing for the launch of this drug so that it can be used for treatment as soon as possible."

nAMD is a disease in which age-related choroidal neovascularization grows under the retina, causing leakage of fluid and blood, resulting in retinal edema and fluid retention that leads to visual impairment. It is one of the leading causes of vision loss in people over the age of 60 worldwide, with an estimated 880,000 patients in Japan[1]. DME is one of the complications of diabetic retinopathy and is estimated to affect more than 710,000 people in Japan[2]. Leakage of plasma components from blood vessels in the retina causes edema in the macula, resulting in visual impairment and sometimes vision loss.

Vabysmo is designed to inhibit two distinct pathways involved in many retinal diseases by blocking the actions of vascular endothelial growth factor-A (VEGF-A) and angiopoietin-2 (Ang-2)[3]. This approval is based on the results from four global phase III clinical trials (DME: YOSEMITE and RHINE studies, nAMD: TENAYA and LUCERNE studies). These trials demonstrated non-inferiority of Vabysmo to an

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existing drug (aflibercept) and met their primary endpoints. In addition, for the first time in a phase III clinical trial of an intravitreal injection, Vabysmo achieved a treatment duration of up to 16 weeks interval. Adverse events in the study eye that occurred at a frequency of 0.5% or greater included intraocular inflammation (e.g., uveitis), intraocular pressure increased, retinal pigment epithelial tears, and vitreous floaters.

[Approval Information]
Product name: VABYSMO ® for Intravitreal Injection 120 mg/ mL
Generic name: faricimab (genetical recombination)
Indications:
・ age-related macular degeneration associated with subfoveal choroidal neovascularization
・ diabetic macular edema
Dosage and administration:
< age-related macular degeneration associated with subfoveal choroidal neovascularization >
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 number of injections can be decreased 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.
< diabetic macular edema >
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 number of injections can be decreased appropriately according to the patient's symptoms. Then, 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.

[Reference]
・YOSEMITE and RHINE studies
Roche's faricimab meets primary endpoint and shows strong durability across two global phase III studies for diabetic macular edema, a leading cause of blindness (Press release by Roche issued on December 21, 2020)
https://www.roche.com/media/releases/med-cor-2020-12-21.htm

・TENAYA and LUCERNE studies
Roche's faricimab meets primary endpoint in two global phase III studies and shows potential to extend time between treatments up to 16 weeks for people with neovascular age-related macular degeneration (Press release by Roche issued on January 25, 2021)
https://www.roche.com/media/releases/med-cor-2021-01-25.htm

New phase III data show Roche's faricimab is the first investigational injectable eye medicine to extend time between treatments up to four months in two leading causes of vision loss, potentially reducing treatment burden for patients (Press release by Roche issued on February 12, 2021)
https://www.roche.com/media/releases/med-cor-2021-02-12.htm

Chugai Files New Drug Application in Japan for Faricimab, the First Bispecific Antibody in Ophthalmology for Diabetic Macular Edema and Neovascular Age-related Macular Degeneration (June 11, 2021)
https://www.chugai-pharm.co.jp/english/news/detail/20210611170000_829.html

About Vabysmo (faricimab)
Vabysmo (faricimab) is the first investigational bispecific antibody designed for the eye.[4)] It targets two distinct pathways – via angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A) – that drive a number of retinal conditions.[5)] Ang-2 and VEGF-A contribute to vision loss by destabilizing blood vessels, causing new leaky blood vessels to form and increasing inflammation.[3)] By simultaneously blocking both pathways involving Ang-2 and VEGF-A, Vabysmo is designed to stabilize blood vessels, potentially improving vision outcomes for longer for people living with retinal conditions.[3)]

About neovascular age-related macular degeneration (nAMD)
Age-related macular degeneration (AMD) is a condition that affects the part of the eye that provides sharp, central vision needed for activities like reading.[6)] Neovascular or "wet" AMD (nAMD) is an advanced form of the disease that can cause rapid and severe vision loss.[7,8)] It develops when new and abnormal blood vessels grow uncontrolled under the macula, causing swelling, bleeding and/or fibrosis.[8)] Worldwide, around 20 million people are living with nAMD – the leading cause of vision loss in people over the age of 60 – and the condition will affect even more people around the world as the global population ages.[6,9,10)]

About diabetic macular edema (DME)
Affecting around 21 million people globally, diabetic macular edema (DME) is a vision-threatening complication of diabetic retinopathy (DR).[11)] DR occurs when damage to blood vessels and the formation of new blood vessels causes blood and/or fluid to leak into the retina – a part of the eye that sends information to the brain, enabling sight.[12)] This leads to swelling, as well as blockage of blood supply to some areas of the retina.[13)] DME occurs when the damaged blood vessels leak into and cause swelling in the macula – the central area of the retina responsible for the sharp vision needed for reading and driving.[12,14)] The number of people with DME is expected to grow as the prevalence of diabetes increases.[15)] The condition is associated with blindness when left untreated and decreased quality of life.[12,16)] There remains a significant unmet need for more effective, longer-lasting therapies for people with DME.[3)]

About the TENAYA and LUCERNE Studies[17)]
TENAYA (NCT03823287) and LUCERNE (NCT03823300) are two identical, randomized, multicenter, double-masked, global phase III studies evaluating the efficacy and safety of Vabysmo compared to aflibercept in 1,329 people living with neovascular age-related macular degeneration (671 in TENAYA and 658 in LUCERNE). The studies each have two treatment arms: Vabysmo 6.0 mg administered at fixed intervals of every 8, 12, or 16 weeks, selected based on objective assessment of disease activity at weeks 20 and 24 after loading period; and aflibercept 2.0 mg administered at fixed 8-week intervals. In both arms, sham injections were administered at study visits when treatment injections were not scheduled, to

maintain the masking of investigators and participants.

The primary endpoint of the studies is the average change in best-corrected visual acuity (BCVA) score (the best distance vision a person can achieve – including with correction such as glasses – when reading letters on an eye chart) from baseline through week 48. Secondary endpoints include: safety; the percentage of participants in the Vabysmo arm receiving treatment every 8, 12, and 16 weeks; the percentage of participants achieving a gain, and the percentage avoiding a loss, of 15 letters or more in BCVA from baseline over time; and change in central subfield thickness (CST) from baseline over time.

About the YOSEMITE and RHINE Studies[18)]

YOSEMITE (NCT03622580) and RHINE (NCT03622593) are two identical, randomized, multicenter, double-masked, global phase III studies evaluating the efficacy and safety of Vabysmo compared to aflibercept in 1,891 people with diabetic macular edema (940 in YOSEMITE and 951 in RHINE). The studies each have three treatment arms: Vabysmo 6.0 mg administered up to every 16 weeks after four initial monthly doses using a treat and extend approach; Vabysmo 6.0 mg administered at 8- week intervals after six initial monthly doses; and aflibercept administered at fixed 8-week intervals after five initial monthly doses. Dosing schedule for patients within the treat-and-extend arm was determined by central subfield thickness (CST) and visual acuity. In all three arms, sham injections were administered at study visits when treatment injections were not scheduled to maintain the masking of investigators and participants.

The primary endpoint of the studies is the average change in BCVA score from baseline at one year, averaged over weeks 48, 52 and 56. Secondary endpoints include: safety; the percentage of participants in the treat and extend arm receiving Vabysmo every 4, 8, 12 and 16 weeks, at week 52; the percentage of participants achieving a two-step or greater improvement from baseline in diabetic retinopathy severity at week 52; the percentage of participants achieving a gain, and the percentage avoiding a loss, of 15 letters or more in BCVA from baseline over time; change in CST from baseline over time; and percentage of patients with absence of intraretinal fluid over time.

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