PACK INSERT FOR MALAYSIA

VABYSMO ® 6MG/0.05ML
SOLUTION FOR INTRAVITREAL INJECTION

Faricimab

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Pharmacotherapeutic group: Ophthalmologicals/Other ocular vascular disorder agents

ATC code: S01LA09

1.2 TYPE OF DOSAGE FORM

Solution for injection

1.3 ROUTE OF ADMINISTRATION

Intravitreal

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile Product

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient(s): faricimab

Excipients: L-Histidine, Acetic Acid 30%, L-Methionine, Sodium Chloride, D-Sucrose, Polysorbate 20, Water for Injection

VABYSMO for injection is a clear to opalescent, colorless to brownish-yellow solution in a single-dose glass vial, containing 28.8 mg faricimab in 0.24 mL solution. This provides a usable amount to deliver a single dose of 0.05 mL solution containing 6 mg of faricimab.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

VABYSMO is indicated for the treatment of adult patients with:

- Neovascular (wet) age-related macular degeneration (nAMD)
- Diabetic macular edema (DME)
- visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).

2.2 DOSAGE AND ADMINISTRATION

This medicinal product must be administered by a qualified physician experienced in intravitreal injections. Each vial should only be used for the treatment of a single eye.

<u>Posology</u>

<u>Neovascular (wet) age-related macular degeneration (nAMD)</u>

The recommended dose is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses.

Thereafter, an assessment of disease activity based on anatomic and/or visual outcomes is recommended 16 and/or 20 weeks after treatment initiation so that treatment can be individualised. In patients without disease activity, administration of faricimab every 16 weeks (4 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) or 12 weeks (3 months) should be considered. There is limited safety data on treatment intervals of 8 weeks or less between injections. Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion, but there is no requirement for monthly monitoring between injections.

Visual impairment due to diabetic macular oedema (DME) and macular oedema secondary to retinal vein occlusion (RVO)

The recommended dose is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly); 3 or more consecutive, monthly injections may be needed.

Thereafter, treatment is individualised using a treat-and-extend approach. Based on the physician’s judgement of the patient’s anatomic and/or visual outcomes, the dosing interval may be extended, in increments of up to 4 weeks. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reduction should be implemented if anatomic and/or visual outcomes deteriorate (see section 3.1). Treatment intervals shorter than 4 weeks and longer than 4 months between injections have not been studied. Monitoring between the dosing visits should be scheduled based on the patient’s status and at the physician’s discretion but there is no requirement for monthly monitoring between injections.

<u>Duration of treatment</u>

This medicinal product is intended for long-term treatment. If visual and/or anatomic outcomes indicate that the patient is not benefitting from continued treatment, treatment should be discontinued.

<u>Delayed or missed dose</u>

If a dose is delayed or missed, the patient should return to be assessed by physician at the next available visit and continue dosing depending on physician’s discretion.

2.2.1 <u>Special populations</u>

Elderly
No dose adjustment is required in patients aged 65 years or above (see *section 3.2.1 Pharmacokinetics in Special Populations*). Safety data in nAMD and RVO patients ≥ 85 years is limited (see *section 2.4 Warning and Precautions*).

Renal impairment
No dose adjustment is required in patients with renal impairment (see *section 3.2.1 Pharmacokinetics in Special Populations*).

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment (see *section 3.2.1 Pharmacokinetics in Special Populations*).

Paediatric population
There is no relevant use of this medicinal product in the paediatric population for the indications of nAMD, DME and RVO.

<u>Method of administration</u>

For intravitreal use only.

VABYSMO should be inspected visually for particulate matter and discoloration prior to administration, and if present, the vial should not be used.

The intravitreal injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, a sterile drape and a sterile eyelid speculum (or equivalent). The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see *section 2.6 Undesirable Effects*). Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

The injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 mL is then delivered slowly; a different scleral site should be used for subsequent injections.

After injection, any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. vision loss, eye pain, redness of the eye, photophobia, blurring of vision) without delay.

For instructions on handling of the medicinal product before administration, refer to instruction for use.

2.3 CONTRAINDICATIONS

VABYSMO is contraindicated in patients with ocular or periocular infections.

VABYSMO is contraindicated in patients with active intraocular inflammation.

VABYSMO is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

2.4 WARNINGS AND PRECAUTIONS

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

Intravitreal injection-related reactions

Intravitreal injections, including those with faricimab, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see *section 2.6 Undesirable Effects*). Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms, such as pain, loss of vision, photophobia, blurred vision, floaters, or redness, suggestive of endophthalmitis or any of the above-mentioned adverse reactions without delay, to permit prompt and appropriate management. Patients with increased frequency of injections may be at increased risk of procedural complications.

Intraocular pressure increases

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including those with faricimab (see *section 2.6 Undesirable Effects*). Special precaution is needed in patients with poorly controlled glaucoma (do not inject VABYSMO while the IOP is ⩾ 30 mmHg). In all cases, both the IOP and perfusion of the optic nerve head must be monitored and managed appropriately.

Systemic effects

Systemic adverse events including arterial thromboembolic events have been reported following intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors and there is a theoretical risk that these may be related to VEGF inhibition. A low incidence rate of arterial thromboembolic events was observed in the faricimab clinical trials in patients with nAMD, DME and RVO. There are limited data on the safety of faricimab treatment in DME patients with high blood pressure (⩾140/90 mmHg) and vascular disease, and in nAMD and RVO patients ⩾ 85 years of age.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with faricimab (see section 2.6). Patients should be instructed to inform their physician of any signs or symptoms of intraocular inflammation such as vision loss, eye pain, increased sensitivity to light, floaters or worsening eye redness, which might be a clinical sign attributable to hypersensitivity against faricimab (see *section 2.6 Undesirable Effects*).

Bilateral treatment

The safety and efficacy of faricimab administered in both eyes concurrently have not been studied. Bilateral treatment could cause bilateral ocular adverse reactions and/or potentially lead to an increase in systemic exposure, which could increase the risk of systemic adverse reactions. Until data for bilateral use become available, this is a theoretical risk for faricimab.

Concomitant use of other anti-VEGF

There are no data available on the concomitant use of faricimab with anti-VEGF medicinal products in the same eye. Faricimab should not be administered concurrently with other anti-VEGF medicinal products (systemic or ocular).

Withholding treatment

Treatment should be withheld in patients with:
- Rhegmatogenous retinal detachment, stage 3 or 4 macular holes, retinal break; treatment should not be resumed until an adequate repair has been performed.
- Treatment related decrease in Best Corrected Visual Acuity (BCVA) of ⩾ 30 letters compared with the last assessment of visual acuity; treatment should not be resumed earlier than the next scheduled treatment.
- An intraocular pressure of ⩾ 30 mmHg.
- A subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ⩾ 50%, of the total lesion area.
- Performed or planned intraocular surgery within the previous or next 28 days; treatment should not be resumed earlier than the next scheduled treatment.

Retinal pigment epithelial tear

Retinal pigment epithelial (RPE) tear is a complication of pigment epithelial detachment (PED) in patients with nAMD. Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for nAMD, include a large and/or high pigment epithelial detachment. When initiating faricimab therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears. RPE tears are common in nAMD patients with PED, treated with intravitreal anti-VEGF agents including faricimab. There was a higher rate of RPE tear in the faricimab group (2.9%) compared to aflibercept group (1.5%). The majority of events occurred during the loading phase, and were mild to moderate, without impact on vision.

Populations with limited data

There is only limited experience in the treatment of nAMD and RVO patients ⩾ 85 years, and DME patients with type I diabetes, patients with HbA1c over 10%, patients with high-risk proliferative diabetic retinopathy (DR), high blood pressure (⩾ 140/90 mmHg) and vascular disease, sustained dosing intervals shorter than every 8 weeks (Q8W), or nAMD, DME and RVO patients with active systemic infections. There is limited safety information on sustained dosing intervals of 8 weeks or less and these may be associated with a higher risk of ocular and systemic adverse reactions, including serious adverse reactions. There is also no experience of treatment with faricimab in diabetic or RVO patients with uncontrolled hypertension and patients with RVO who have failed previous therapy. This lack of information should be considered by the physician when treating such patients.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

2.4.1 Drug Abuse and Dependence

There is no evidence that VABYSMO has the potential for drug abuse and dependence.

2.4.2 Ability to Drive and Use Machines

VABYSMO may have a minor influence on the ability to drive and use machines due to possible temporary visual disturbances following the intravitreal injection and the associated eye examination. Patients should not drive or use machines until visual function has recovered sufficiently.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

Fertility

No reproductive or fertility studies have been conducted. No effects on reproductive organs or fertility were observed in a 6-month cynomolgus monkey study with VABYSMO. VEGF inhibition has been shown to affect follicular development, corpus luteum function and fertility. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development, however the risk is considered low due to the low systemic exposure after ocular administration (*see section 3.3.3 Impairment of Fertility*).

Contraception

Women of childbearing potential should use contraception during treatment with VABYSMO and for at least 3 months following the last dose of VABYSMO.

2.5.2 Pregnancy

There are no or limited amount of data from the use of faricimab in pregnant women. The systemic exposure to faricimab is low after ocular administration, but due to its mechanism of action (i.e. VEGF inhibition), faricimab must be regarded as potentially teratogenic and embryo-/foetotoxic (see *section 3.3 Nonclinical Safety*).

Faricimab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Labor and Delivery

The safe use of VABYSMO during labor and delivery has not been established.

2.5.3 Lactation

It is not known whether VABYSMO is excreted in human breast milk. No studies have been conducted to assess the impact of VABYSMO on milk production or its presence in breast milk. Because many drugs are excreted in human milk with the potential for absorption and harm to infant growth and development exists, caution should be exercised when VABYSMO is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO.

2.5.4 Pediatric Use

The safety and efficacy of VABYSMO in pediatric patients have not been established.

2.5.5 Geriatric Use

In the six Phase III clinical studies, approximately 58% (1,496/2,571) of patients randomized to treatment with VABYSMO were ⩾ 65, years of age. No significant differences in efficacy or safety of VABYSMO were seen with increasing age in these studies (*see sections 2.2.1 Special Populations and 3.2.1 Pharmacokinetics in Special Populations*).

2.5.6 Renal Impairment

No dose adjustment is required in patients with renal impairment (*see sections 2.2.1 Special Populations and 3.2.1 Pharmacokinetics in Special Populations*).

2.5.7 Hepatic Impairment

The safety and efficacy of VABYSMO in patients with hepatic impairment has not been studied (*see sections 2.2.1 Special Dosage Instructions and 3.2.1 Pharmacokinetics in Special Populations*).

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

Summary of the safety profile

A total of 4,489 patients constituted the safety population in the six Phase III clinical studies (2,567 VABYSMO treated patients; 664 in nAMD, 1,262 in DME and 641 in RVO).

The most serious adverse reactions were uveitis (0.5%), endophthalmitis (0.4%), vitritis (0.4%), retinal tear (0.2%), rhegmatogenous retinal detachment (0.1%) and traumatic cataract (< 0.1%).

The most frequently reported adverse reactions in patients treated with VABYSMO were cataract (10%), conjunctival hemorrhage (7%), vitreous detachment (4%), IOP increased (4%), vitreous floaters (4%), eye pain (3%) and retinal pigment epithelial tear (nAMD only) (3%).

Tabulated summary of adverse drug reactions from clinical trials

The safety data described below include all adverse reactions from the pooled data across six Phase III clinical studies in the indications nAMD and DME, and RVO with a reasonable possibility of causality attribution to the injection procedure or medicinal product.

The adverse reactions are listed according to the MedDRA system organ class and ranked by frequency using the following convention: very common (⩾ 1/10), common (⩾ 1/100 to < 1/10), uncommon (⩾ 1/1,000 to < 1/100), rare (⩾ 1/10,000 to < 1/1,000).

Table 1: Summary of adverse reactions occurring in patients treated with VABYSMO in phase III clinical trials

Adverse reactions	VABYSMO N = 2,567	Frequency category
Eye Disorders		
Cataract	9.7%	Common
Conjunctival hemorrhage	6.7%	Common
Vitreous detachment	4.2%	Common
Intraocular pressure increased	3.5%	Common
Vitreous floaters	3.5%	Common
RPE tear (nAMD only)	2.9%	Common
Eye pain	2.5%	Common
Corneal abrasion	0.9%	Uncommon
Eye irritation	0.8%	Uncommon
Lacrimation increased	0.8%	Uncommon
Eye pruritus	0.7%	Uncommon
Ocular discomfort	0.7%	Uncommon
Ocular hyperemia	0.7%	Uncommon
Vision blurred	0.7%	Uncommon
Iritis	0.6%	Uncommon
Visual acuity reduced	0.6%	Uncommon
Uveitis	0.5%	Uncommon
Endophthalmitis	0.4%	Uncommon
Sensation of foreign body	0.4%	Uncommon
Vitreous hemorrhage	0.4%	Uncommon
Vitritis	0.4%	Uncommon
Iridocyclitis	0.3%	Uncommon
Conjunctival hyperamia	0.2%	Uncommon
Procedural pain	0.2%	Uncommon
Retinal tear	0.2%	Uncommon
Rhegmatogenous retinal detachment	0.1%	Uncommon
Traumatic cataract	<0.1%	Rare
Visual acuity reduced transiently	< 0.1%	Rare

Description of selected adverse drug reactions from clinical trials

There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the VABYSMO clinical trials in patients with nAMD, DME and RVO. Across indications no notable difference between the groups treated with VABYSMO and the comparator were observed.

Immunogenicity

There is a potential for an immune response in patients treated with faricimab (see *section 2.4 Warning and Precautions*). After dosing with faricimab for up to 112 (nAMD), 100 (DME) and 72 (RVO) weeks, treatment-emergent anti-faricimab antibodies were detected in approximately 13.8%, 9.6% and 14.4% of patients with nAMD, DME, and RVO randomized to faricimab, respectively. The clinical significance of anti-faricimab antibodies on safety is unclear at this time. The incidence of intraocular inflammation in anti-faricimab antibody positive patients was 12/98 (12.2%; nAMD), 15/128 (11.7%; DME) and 9/95 (9.5%; RVO) and in anti-faricimab antibody negative patients was 8/562 (1.4%; nAMD), 5/1124 (0.4%; DME) and 10/543 (1.8%; RVO). The incidence of serious ocular adverse reactions in anti-faricimab antibody positive patients was 6/98 (6.1%; nAMD), 14/128 (10.9%; DME) and 7/95 (7.4%; RVO), and in anti-faricimab antibody negative patients was 23/562 (4.1%; nAMD), 45/1124 (4.0%; DME) and 34/543 (6.3%; RVO). Anti-faricimab antibodies were not associated with an impact on clinical efficacy or systemic pharmacokinetics.

2.6.2 Postmarketing Experience

Rare cases of retinal vasculitis and/or retinal occlusive vasculitis have been spontaneously reported in the post-marketing setting. Retinal vasculitis and retinal occlusive vasculitis have also been reported in patients treated with IVT therapies.

Eye disorders: retinal vasculitis, retinal occlusive vasculitis.

2.7 OVERDOSE

Doses higher than the recommended dosing regimen have not been studied. Overdosing with greater than recommended injection volume may increase intraocular pressure.

In the event of an overdose, IOP should be monitored and, if deemed necessary by the treating physician, appropriate treatment should be initiated.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed. Based on the biotransformation and elimination of faricimab (see *section 3.2 Pharmacokinetic Properties*), no interactions are expected. However, faricimab should not be administered concurrently with other systemic or ocular anti-VEGF medicinal products (see *section 2.4 Warning and Precautions*).

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

Faricimab is a humanized bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralization of both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A).

Ang-2 causes vascular instability by promoting endothelial destabilization, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitizes blood vessels to the activity of VEGF-A resulting in further vascular destabilization. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularization.

By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability.

Pharmacodynamics

A suppression from baseline of median ocular free Ang-2 and free VEGF-A concentrations was observed from day 7 onwards in the six Phase III clinical studies.

nAMD

In Phase III studies in patients with nAMD (TENAYA, LUCERNE), objective, pre-specified visual and anatomic criteria, as well as treating physician clinical assessment, were used to guide treatment decisions at the disease activity assessment time points (week 20 and week 24).

Reductions in mean central subfield thickness (CST) were observed from baseline through week 48 with VABYSMO and were comparable to those observed with aflibercept. The mean CST reduction from baseline to the primary endpoint visits (averaged at weeks 40-48) was -137 µm and -137 µm for VABYSMO dosed up to every 16 weeks (Q16W) versus -129 µm and -131 µm with aflibercept, in TENAYA and LUCERNE, respectively. These mean CST reductions were maintained through year 2.

There was a comparable effect of VABYSMO and aflibercept on the reduction of intraretinal fluid (IRF), subretinal fluid (SRF), and pigment epithelial detachment (PED). At the primary endpoint visits (min-max, weeks 40-48), the proportion of patients in TENAYA and LUCERNE, respectively, with absence of IRF was: 76%-82% and 78%-85% in VABYSMO vs. 74%-85% and 78%-84% in aflibercept; absence of SRF: 70%-79% and 66%-78% in VABYSMO vs. 66%-78% and 62%-76% in aflibercept; absence of PED: 3%-8% and 3%-6% in VABYSMO vs. 8%-10% and 7%-9% in aflibercept. These reductions in IRF, SRF, and PED were maintained at year 2 (weeks 104-108).

At week 48, there was comparable change in total CNV lesion area from baseline across treatment arms (0.0 mm^2 and 0.4 mm^2 in VABYSMO vs. 0.4 mm^2 and 1.0 mm^2 in aflibercept, in TENAYA and LUCERNE, respectively). There was a comparable reduction in CNV leakage area from baseline across treatment arms (-3.8 mm^2 and -3.2 mm^2 in VABYSMO and -3.0 mm^2 and -2.2 mm^2 in aflibercept, in TENAYA and LUCERNE, respectively).

DME

In Phase III studies in patients with DME (YOSEMITE and RHINE), anatomic parameters related to macular edema were part of the disease activity assessments guiding treatment decisions.

The reductions in mean CST from baseline were numerically greater in patients treated with VABYSMO every 8 weeks (Q8W) and VABYSMO up to Q16W adjustable dosing as compared to aflibercept Q8W from week 4 to week 100 in both YOSEMITE and RHINE. Greater proportions of patients in both VABYSMO arms achieved absence of IRF and absence of DME (defined as reaching CST below 325 µm) as measured on Spectral Domain Optical Coherence Tomography (SD-OCT) over time in both studies, compared to the aflibercept arm. Comparable reductions in SRF were observed across both VABYSMO and aflibercept treatment arms over time in both studies.

The mean reduction of CST from baseline to the primary endpoint visits (averaged at weeks 48-56) was 207 µm and 197 µm in patients treated with VABYSMO Q8W and VABYSMO up to Q16W adjustable dosing as compared to 170 µm in aflibercept Q8W patients in YOSEMITE; results were 196 µm, 188 µm and 170 µm, respectively in RHINE. These mean CST reductions were maintained through year 2. The proportion of patients with absence of DME at primary endpoint visits (min-max, weeks 48-56) were 77%-87% and 80%-82% in patients treated with VABYSMO Q8W and VABYSMO up to Q16W adjustable dosing, as compared to 64%-71% in aflibercept Q8W patients in YOSEMITE; results were 85%-90%, 83%-87%, and 71%-77%, respectively in RHINE. These results were maintained through year 2.

At week 16, the proportion of patients with absence of IRF was numerically greater in patients receiving VABYSMO Q8W or VABYSMO up to Q16W adjustable dosing versus aflibercept Q8W dosing in both studies (YOSEMITE: 16% and 22% vs. 13%; RHINE: 20% and 20% vs.13%). The proportions of patients with absence of IRF at primary endpoint visits (min-max, weeks 48-56) were 42%-48% and 34%-43% in patients treated with VABYSMO Q8W and VABYSMO up to Q16W adjustable dosing, as compared to 22%-25% in aflibercept Q8W patients in YOSEMITE; results were 39%-43%, 33%-41%, and 23%-29%, respectively in RHINE.

RVO

In Phase III studies in patients with branch retinal vein occlusion (BRVO; BALATON) and central/hemiretinal vein occlusion (C/HRVO; COMINO), reductions in mean CST were observed from baseline to week 24 with VABYSMO every 4 weeks (Q4W) and were comparable to those seen with aflibercept Q4W. The mean CST reduction from baseline to week 24 was 311.4 µm for VABYSMO versus 304.4 µm for aflibercept, and 461.6 µm for

VABYSMO Q4W versus 448.8 µm for aflibercept Q4W, in BALATON and COMINO, respectively. CST reductions were maintained through week 72 when patients moved to a VABYSMO up to Q16W adjustable dosing regimen.

Comparable proportions of patients in both VABYSMO and aflibercept arms achieved absence of IRF, absence of SRF and absence of macular edema (defined as reaching CST below 325 µm) over time through week 24, in both studies. These results were maintained through week 72 when patients moved to a VABYSMO up to Q16W adjustable dosing regimen.

In BALATON, at week 24, the proportion of patients with absence of macular edema was 95.3% in patients treated with VABYSMO Q4W versus 93.9% in patients treated with aflibercept Q4W; the proportion of patients with absence of IRF was 72.5% in patients treated with VABYSMO Q4W versus 66% in patients treated with aflibercept Q4W. The proportion of patients with absence of SRF was 91.3% in patients in the VABYSMO Q4W arm, versus 90.3% in patients in the aflibercept Q4W arm.

In COMINO, at week 24, the proportion of patients with absence of macular edema was 93.7% in patients treated with VABYSMO Q4W versus 92% in patients treated with aflibercept Q4W. The proportion of patients with absence of IRF was 76.2% in patients treated with VABYSMO Q4W versus 70.8% in patients treated with aflibercept Q4W; the proportion of patients with absence of SRF was 96.4% in patients treated with VABYSMO Q4W versus 93.4% in patients treated with aflibercept Q4W.

3.1.2 Clinical / Efficacy Studies

Treatment of nAMD

The safety and efficacy of VABYSMO (faricimab) were assessed in two randomized, multi-center, double-masked, active comparator-controlled studies in patients with nAMD, TENAYA (NCT03823287) and LUCERNE (NCT03823300). A total of 1,329 patients were enrolled in these studies, with 1,135 (85%) patients completing the studies through week 112. A total of 1,326 patients received at least one dose (664 with VABYSMO). Patient ages ranged from 50 to 99 with a mean of 75.9 years.

In both studies, patients were randomized in a 1:1 ratio to one of two treatment arms:

- VABYSMO 6 mg up to Q16W after four initial monthly doses
- Aflibercept 2 mg Q8W after three initial monthly doses

After the first four monthly doses (weeks 0, 4, 8, and 12) patients randomized to the VABYSMO arm received Q16W, every 12 weeks (Q12W) or Q8W dosing based on an assessment of disease activity at weeks 20 and 24, using objective pre-specified visual and anatomic criteria as well as treating physician clinical assessment. Patients remained on these fixed dosing intervals until week 60 without supplemental therapy. From Week 60 onwards, patients in the VABYSMO arm moved to an adjustable dosing regimen, where the dosing interval could be increased in up to 4-week increments (up to Q16W) or could be decreased by up to 8-week increments (up to Q8W) based on an automated objective assessment of pre-specified visual and anatomic disease activity criteria. Patients in the aflibercept arm remained on Q8W dosing throughout the study period. Both studies were 112 weeks in duration.

The primary efficacy endpoint was the change from baseline in BCVA based on an average at weeks 40, 44, and 48, measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score. In both studies, VABYSMO up to Q16W treated patients had a comparable mean change from baseline in BCVA, as the patients treated with aflibercept Q8W at year 1. Meaningful vision gains from baseline were seen through week 112 in both treatment arms. Detailed results of both studies are shown in Table 2, Figure 1, and Figure 2 below.

The proportion of patients on each of the different treatment intervals at week 48 in TENAYA and LUCERNE, respectively was:

- Q16W: 46%, 45%
- Q12W: 34%, 33%
- Q8W: 20%, 22%

The proportion of patients on each of the different treatment intervals at week 112 in TENAYA and LUCERNE, respectively was:

- Q16W: 59%, 67%
- Q12W: 15%, 14%
- Q8W: 26%, 19%

Table 2: Efficacy outcomes at the primary endpoint visits[a] and at year 2[b] in TENAYA and LUCERNE

Efficacy Outcomes	**TENAYA**				**LUCERNE**			
	Year 1		Year 2		Year 1		Year 2	
	VABYSMO up to Q16W N = 334	Aflibercept Q8W N = 337	VABYSMO up to Q16W N = 334	Aflibercept Q8W N = 337	VABYSMO up to Q16W N = 331	Aflibercept Q8W N = 327	VABYSMO up to Q16W N = 331	Aflibercept Q8W N = 327
Mean change in BCVA as measured by ETDRS letter score from baseline (95% CI)	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	3.7 (2.1, 5.4)	3.3 (1.7, 4.9)	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)	5.0 (3.4, 6.6)	5.2 (3.6, 6.8)
Difference in LS mean (95% CI)	0.7 (-1.1, 2.5)		0.4 (-1.9, 2.8)		0.0 (-1.7, 1.8)		-0.2 (-2.4, 2.1)	
Proportion of patients with ⩾ 15 letter gain from baseline (CMH weighted proportion, 95% CI)	20.0% (15.6%, 24.4%)	15.7% (11.9%, 19.6%)	22.5% (17.8%, 27.2%)	16.9% (12.7%, 21.1%)	20.2% (15.9%, 24.6%)	22.2% (17.7%, 26.8%)	22.4% (17.8%, 27.1%	21.3% (16.8%, 25.9%)
Difference in CMH weighted % (95% CI)	4.3% (-1.6%, 10.1%)		5.6% (-0.7%, 11.9%)		-2.0% (-8.3%, 4.3%)		1.1% (-5.4%, 7.6%)	
Proportion of patients avoiding ⩾ 15 letter loss from baseline (CMH weighted	95.4% (93.0%, 97.7%)	94.1% (91.5%, 96.7 %)	92.1% (89.1%, 95.1%)	88.6% (85.1%, 92.2%)	95.8% (93.6%, 98.0%)	97.3% (95.5%, 99.1%)	92.9% (90.1%, 95.8%)	93.2% (90.2%, 96.2%)

proportion,95 % CI)								
Difference in CMH weighted % (95% CI)	1.3% (-2.2%, 4.8%)		3.4% (-1.2%, 8.1%)		-1.5% (-4.4%, 1.3%)		-0.2% (-4.4%, 3.9%)	

[a]Average of weeks 40, 44 and 48; [b]Average of weeks 104, 108, 112

BCVA: Best Corrected Visual Acuity

ETDRS: Early Treatment Diabetic Retinopathy Study

CI: Confidence Interval

LS: Least Square

CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.

Figure 1: Mean change in visual acuity from baseline to week 112 in TENAYA

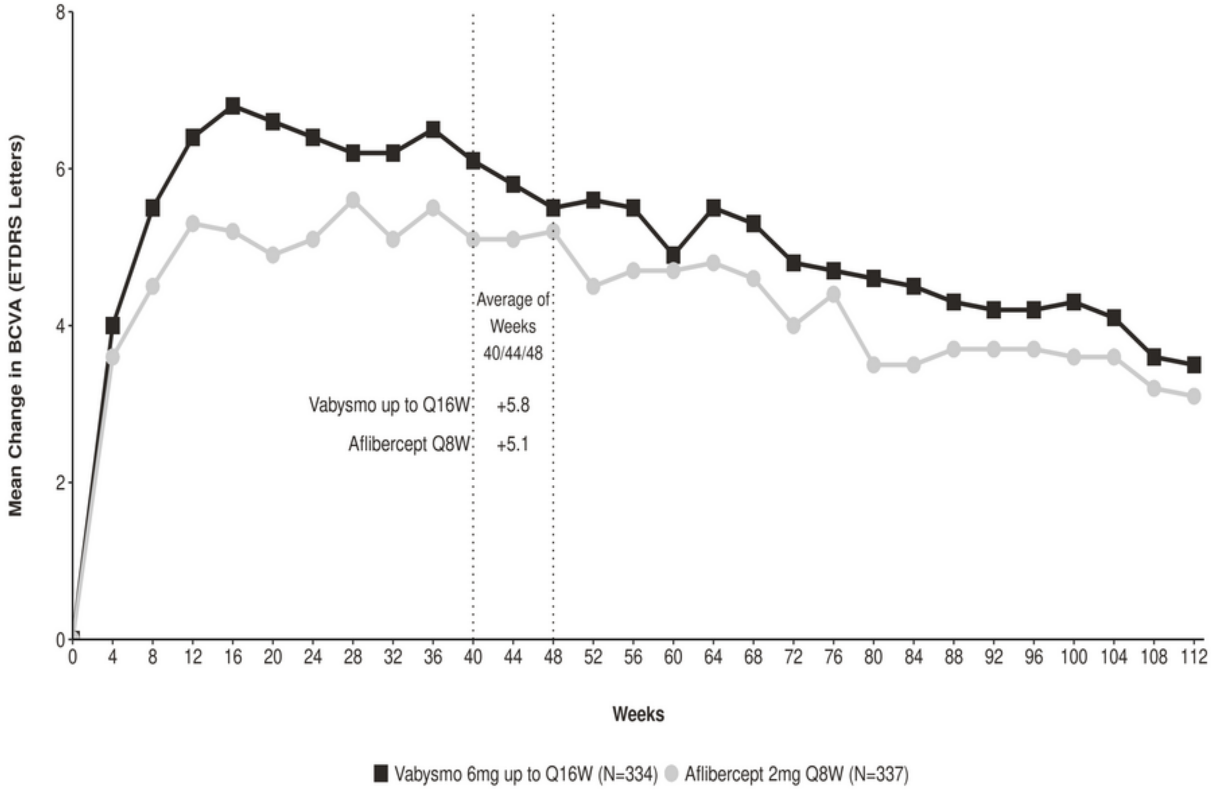
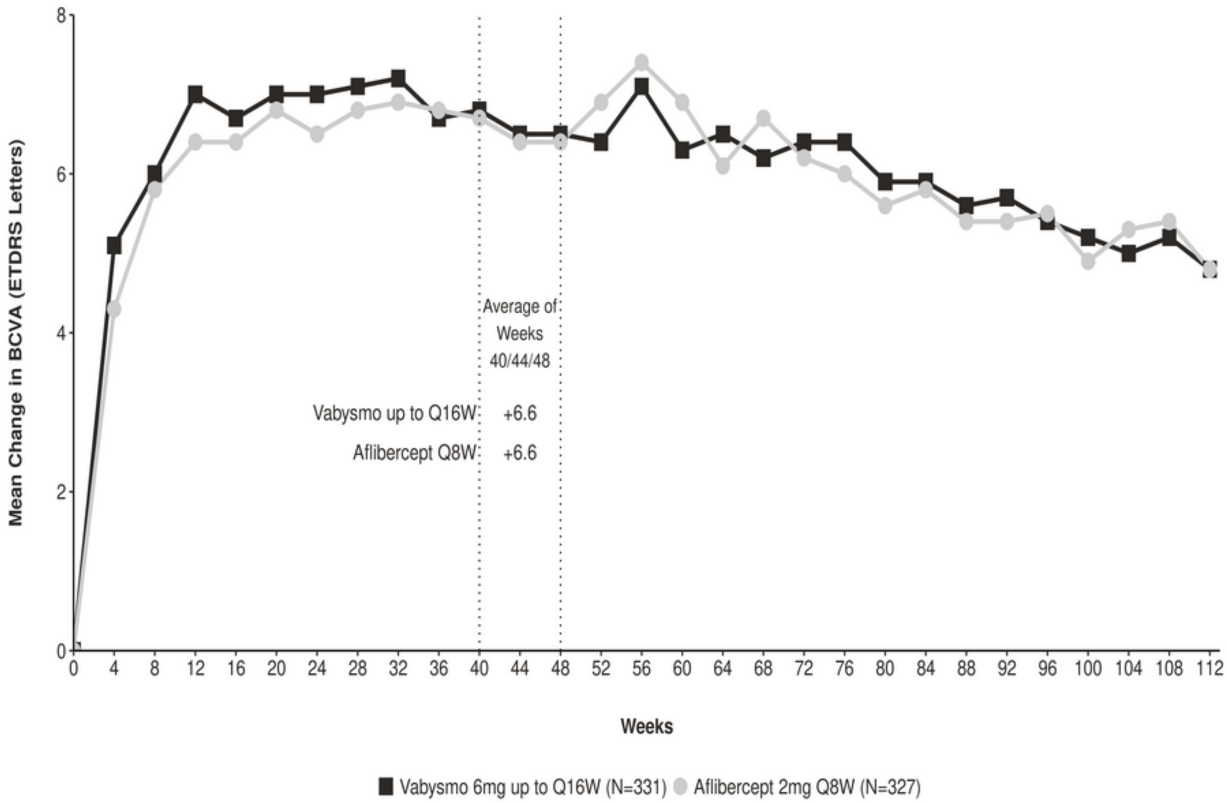


Figure 2: Mean change in visual acuity from baseline to week 112 in LUCERNE



In both TENAYA and LUCERNE, improvements from baseline in BCVA and CST at week 60 were comparable across the two treatment arms and consistent with those seen at week 48.

At Week 60, 46% of patients in TENAYA and LUCERNE were on a Q16W interval. Of these, 69% patients in both studies maintained Q16W through Week 112 without an interval reduction.

At Week 60, 80% and 78% of patients in TENAYA and LUCERNE, respectively, were on a ⩾ Q12W interval (Q16W or Q12W). Of these, 67% and 75% patients, respectively, maintained a ⩾ Q12W interval through Week 112 without an interval reduction below Q12W.

At Week 60, 33% of patients in TENAYA and LUCERNE were on a Q12W interval. Of these, 3.2% and 0% patients in TENAYA and LUCERNE, respectively maintained Q12W through Week 112.

At Week 60, 20% and 22% patients in TENAYA and LUCERNE, respectively, were on a Q8W interval. Of these, 34% and 30% in TENAYA and LUCERNE, respectively, maintained Q8W therapy through Week 112.

Efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, lesion type, lesion size) in each study, and in the pooled analysis, were consistent with the results in the overall populations.

In both studies, VABYSMO up to Q16W demonstrated clinically meaningful improvements from baseline to week 48 in the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) composite score that was comparable to aflibercept Q8W. Patients in VABYSMO arms in TENAYA and LUCERNE achieved a ⩾ 4 point improvement from baseline in the NEI VFQ -25 composite score at week 48. These results were maintained at week 112.

Treatment of DME

The safety and efficacy of VABYSMO were assessed in two randomized, multi-centre, double-masked, active comparator-controlled 2-year studies (YOSEMITE and RHINE) in patients with DME. A total of 1,891 patients were enrolled in the two studies with 1,622 (86%) patients completing the studies through week 100. A total of 1,887 patients were treated with at least one dose through week 56 (1,262 with VABYSMO). Patient ages ranged from 24 to 91 with a mean of 62.2 years. The overall population included both anti-VEGF naive patients (78%) and patients who had been previously treated with a VEGF inhibitor prior to study participation (22%). In both studies, patients were randomized in a 1:1:1 ratio to one of the three treatment regimens:

- VABYSMO 6 mg Q8W after the first 6 monthly doses.

- VABYSMO 6 mg up to Q16W adjustable dosing administered in 4, 8, 12 or 16 week intervals after the first 4 monthly doses.

- Aflibercept 2 mg Q8W after the first 5 monthly doses.

In the Q16W adjustable dosing arm, the dosing interval could be increased in 4-week increments or could be decreased in 4- or 8-week increments based on automated objective assessment of pre-specified visual and anatomic disease activity criteria.

Both studies demonstrated efficacy in the primary endpoint, defined as the change from baseline in BCVA at year 1 (average of the week 48, 52, and 56 visits) as measured by the ETDRS Letter Score. In both studies, VABYSMO up to Q16W treated patients had a comparable mean change from baseline in BCVA, as the patients treated with aflibercept Q8W at year 1, and these vision gains were maintained through year 2. Detailed results of both studies are shown in Table 3, Figure 3, and Figure 4 below.

After 4 initial monthly doses, the patients in the VABYSMO up to Q16W adjustable dosing arm could have received between the minimum of 6 and the maximum of 21 total injections through week 96. At week 52, 74% and 71% of patients in the VABYSMO up to Q16W adjustable dosing arm achieved a Q16W or Q12W dosing interval in YOSEMITE and RHINE, respectively (53% and 51% on Q16W, 21% and 20% on Q12W). Of these patients, 75% and 84% maintained ⩾ Q12W dosing without an interval reduction below Q12W through week 96; of the patients on Q16W at week 52, 70% and 82% of patients maintained Q16W dosing without an interval reduction through week 96 in YOSEMITE and RHINE, respectively. At week 96, 78% of patients in the VABYSMO up to Q16W adjustable dosing arm achieved a Q16W or Q12W dosing interval in both studies (60% and 64% on Q16W, 18% and 14% on Q12W). 4% and 6% of patients were extended to Q8W and stayed on ⩽ Q8W dosing intervals through week 96; 3% and 5% received only Q4W dosing in YOSEMITE and RHINE through week 96, respectively.

Detailed results from the analyses of YOSEMITE and RHINE studies are listed in Table 3 and Figures 3 and Figure 4 below.

Table 3: Efficacy outcomes at the year 1 primary endpoint visits[a] and at year 2[b] in YOSEMITE and RHINE

Efficacy Outcomes	YOSEMITE						RHINE					
	Year 1			Year 2			Year 1			Year 2		
	VABYSMO Q8W N = 315	VABYSMO up to Q16W adjustable dosing N = 313	Aflibercept Q8W N = 312	VABYSMO Q8W N = 315	VABYSMO up to Q16W adjustable dosing N = 313	Aflibercept Q8W N = 312	VABYSMO Q8W N = 317	VABYSMO up to Q16W adjustable dosing N = 319	Aflibercept Q8W N = 315	VABYSMO Q8W N = 317	VABYSMO up to Q16W adjustable dosing N = 319	Aflibercept Q8W N = 315
Mean change in BCVA as measured by ETDRS letter score from baseline (97.5% CI year 1 and 95% CI year 2)	10.7 (9.4, 12.0)	11.6 (10.3, 12.9)	10.9 (9.6, 12.2)	10.7 (9.4, 12.1)	10.7 (9.4, 12.1)	11.4 (10.0, 12.7)	11.8 (10.6, 13.0)	10.8 (9.6, 11.9)	10.3 (9.1, 11.4)	10.9 (9.5, 12.3)	10.1 (8.7, 11.5)	9.4 (7.9, 10.8)
Difference in LS mean (97.5% CI year 1 and 95% CI year 2)	-0.2 (-2.0, 1.6)	0.7 (-1.1, 2.5)		-0.7 (-2.6, 1.2)	-0.7 (-2.5, 1.2)		1.5 (-0.1, 3.2)	0.5 (-1.1, 2.1)		1.5 (-0.5, 3.6)	0.7 (-1.3, 2.7)	
Proportion of patients who gained at least 15 letters in BCVA from baseline (CMH weighted proportion, 95% CI year 1 and year 2)	29.2% (23.9%, 34.5%)	35.5% (30.1%, 40.9%)	31.8% (26.6%, 37.0%)	37.2% (31.4%, 42.9%)	38.2% (32.8%, 43.7%)	37.4% (31.7%, 43.0%)	33.8% (28.4%, 39.2%)	28.5% (23.6%, 33.3%)	30.3% (25.0%, 35.5%)	39.8% (34.0%, 45.6%)	31.1% (26.1%, 36.1%)	39.0% (33.2%, 44.8%)

Difference in CMH weighted % (95% CI year 1 and year 2)	-2.6% (-10.0%, 4.9%)	3.5% (-4.0%, 11.1%)		-0.2% (-8.2%, 7.8%)	0.2% (-7.6%, 8.1%)		3.5% (-4.0%, 11.1%)	-2.0% (-9.1%, 5.2%)		0.8% (-7.4%, 9.0%)	-8% (-15.7%, -0.3%)	
Proportion of patients who avoided loss of at least 15 letters in BCVA from baseline (CMH weighted proportion, 95% CI year 1 and year 2)	98.1% (96.5%, 99.7%)	98.6% (97.2%, 100.0%)	98.9% (97.6%, 100.0%)	97.6% (95.7%, 99.5%)	97.8% (96.1%, 99.5%)	98.0% (96.2%, 99.7%)	98.9% (97.6%, 100.0%)	98.7% (97.4%, 100.0%)	98.6% (97.2%, 99.9%)	96.6% (94.4%, 98.8%)	96.8% (94.8%, 98.9%)	97.6% (95.7%, 99.5%)
Difference in CMH weighted % (95% CI year 1 and year 2)	-0.8% (-2.8%, 1.3%)	-0.3% (-2.2%, 1.5%)		-0.4% (-2.9%, 2.2%)	-0.2% (-2.6%, 2.2%)		0.3% (-1.6%, 2.1%)	0.0% (-1.8%, 1.9%)		-1.0% (-3.9%, 1.9%)	-0.7% (-3.5%, 2.0%)	

[a]Average of weeks 48, 52, 56, [b]Average of weeks 92, 96, 100
BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
CI: Confidence Interval
LS: Least Square
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.
Note: CMH weighted % for aflibercept arm presented for VABYSMO Q8W vs. aflibercept comparison, however the corresponding CMH weighted % for VABYSMO adjustable vs. aflibercept comparison is similar to the one shown above.

Figure 3: Mean change in visual acuity from baseline to year 2 (week 100) in YOSEMITE

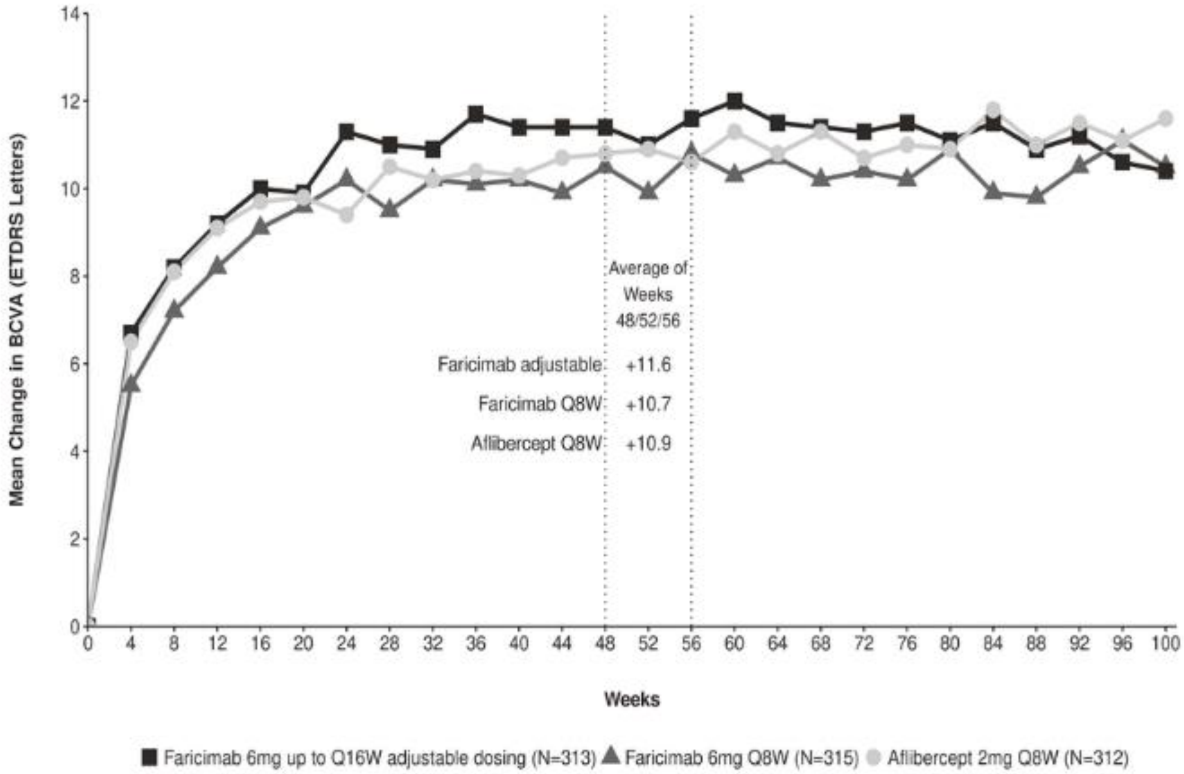
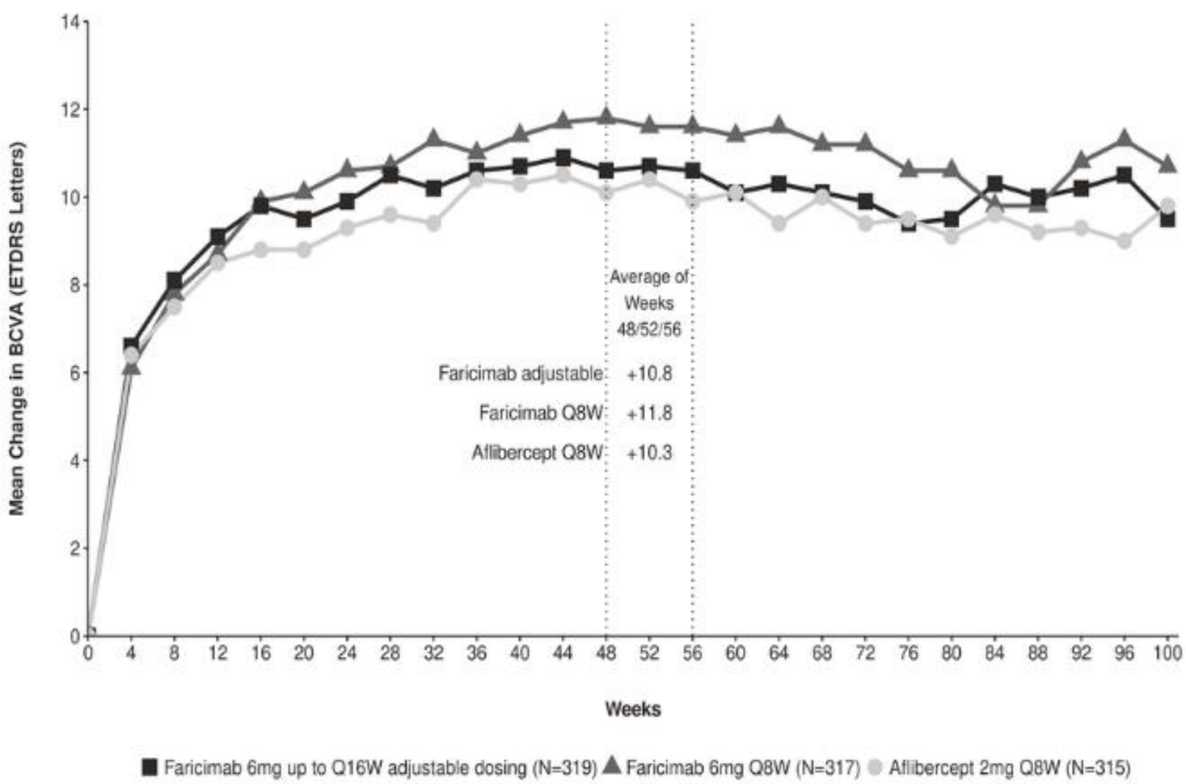


Figure 4: Mean change in visual acuity from baseline to year 2 (week 100) in RHINE



Efficacy results in patients who were anti-VEGF treatment naive prior to study participation and in all the other evaluable subgroups (e.g. by age, gender, race, baseline HbA1c, baseline visual acuity) in each study were consistent with the results in the overall populations.

Across studies, VABYSMO Q8W and up to Q16W adjustable dosing showed improvements in the pre-specified efficacy endpoint of mean change from baseline to week 52 in the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) composite score that was comparable to aflibercept Q8W and exceeded the threshold of 4 points. VABYSMO Q8W and up to Q16W adjustable dosing also demonstrated clinically meaningful improvements in the pre-specified efficacy endpoint of change from baseline to week 52 in the NEI VFQ-25 near activities, distance activities, and driving scores, that were comparable to aflibercept Q8W. The magnitude of these changes corresponds to a 15-letter gain in BCVA. Comparable proportions of patients treated with VABYSMO Q8W, VABYSMO up to Q16W adjustable dosing, and aflibercept Q8W experienced a clinically meaningful improvement of ⩾ 4 points from baseline to week 52 in the NEI VFQ-25 composite score, a pre-specified efficacy endpoint. These results were maintained at week 100.

An additional key efficacy outcome in DME studies was the change in the Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale (ETDRS-DRSS) from baseline to week 52. Of the 1,891 patients enrolled in Studies YOSEMITE and RHINE, 708 and 720 patients were evaluable for DR endpoints, respectively.

The ETDRS-DRSS scores ranged from 10 to 71 at baseline.

The majority of patients, approximately 60%, had moderate to severe non-proliferative DR (DRSS 43/47/53) at baseline.

At week 52, the proportion of patients improving by ⩾ 2 steps on the ETDRS-DRSS was 43% to 46% across the VABYSMO Q8W and VABYSMO adjustable up to Q16W arms in both studies, compared to 36% and 47% in aflibercept Q8W arms of YOSEMITE and RHINE, respectively. The results at week 96 were 43% to 54% across the VABYSMO Q8W and VABYSMO adjustable up to Q16W arms in both studies, compared to 42% and 44% in aflibercept Q8W arms of YOSEMITE and RHINE, respectively.

Comparable results across the treatment arms were observed in both studies in the proportions of patients improving by ⩾ 3 steps on the ETDRS-DRSS from baseline at week 52, and these results were maintained at week 96.

The results from the ⩾ 2-step and ⩾ 3-step ETDRS-DRSS improvement analyses from baseline at week 52 and at week 96 are shown in Table 4 below. The proportion of patients with a ⩾ 2-step improvement on the ETDRS-DRSS at baseline, week 16, week 52 and at week 96 are shown in Figures 5 and 6
below.

Table 4: Proportion of patients who achieved ≥ 2-step and ≥ 3-step improvement from baseline in ETDRS-DRSS score at week 52 and at week 96 in YOSEMITE and RHINE (DR evaluable population)

	YOSEMITE						RHINE					
	52 Weeks			96 Weeks			52 Weeks			96 Weeks		
	VABYSMO Q8W n = 237	VABYSMO up to Q16W adjustable dosing n = 242	Aflibercept Q8W n = 229	VABYSMO Q8W n = 220	VABYSMO up to Q16W adjustable dosing n = 234	Aflibercept Q8W n = 221	VABYSMO Q8W n = 231	VABYSMO up to Q16W adjustable dosing n = 251	Aflibercept Q8W n = 238	VABYSMO Q8W n = 214	VABYSMO up to Q16W adjustable dosing n = 228	Aflibercept Q8W n = 203
Proportion of patients with ⩾2-step ETDRS-DRSS improvement from baseline (CMH weighted proportion)	46.0%	42.5%	35.8%	51.4%	42.8%	42.2%	44.2%	43.7%	46.8%	53.5%	44.3%	43.8%
Weighted Difference (97.5% CI year 1,	10.2% (0.3%, 20.0%)	6.1% (-3.6%, 15.8%)		9.1% (0.0%, 18.2%)	0.0% (-8.9%, 8.9%)		-2.6% (-12.6%, 7.4%)	-3.5% (-13.4%, 6.3%)		9.7% (0.4%, 19.1%)	0.3% (-8.9%, 9.5%)	

95% CI year 2)												
Proportion of patients with ⩾ 3-step ETDRS-DRSS improvement from baseline (CMH weighted proportion)	16.8%	15.5%	14.7%	22.4%	14.6%	20.9%	16.7%	18.9%	19.4%	25.1%	19.3%	21.8%
Weighted Difference (95% CI year 1 and year 2)	2.1% (-4.3%, 8.6%)	0.6% (-5.8%, 6.9%)		1.5% (-6.0%, 9.0%)	-6.7% (-13.6%, 0.1%)		-0.2% (-5.8%, 5.3%)	-1.1% (-8.0%, 5.9%)		3.3% (-4.6%, 11.3%)	-2.7% (-10.2%, 4.8%)	

ETDRS-DRSS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.
CI: Confidence Interval
Note: CMH weighted % for aflibercept arm presented for VABYSMO Q8W vs. aflibercept comparison, however the corresponding CMH weighted % for VABYSMO adjustable vs. aflibercept comparison is similar to the one shown above.

Figure 5: Proportion of patients who achieved ≥ 2-step improvement from baseline in ETDRS-DRSS score at week 16, week 52 and at week 96 in YOSEMITE

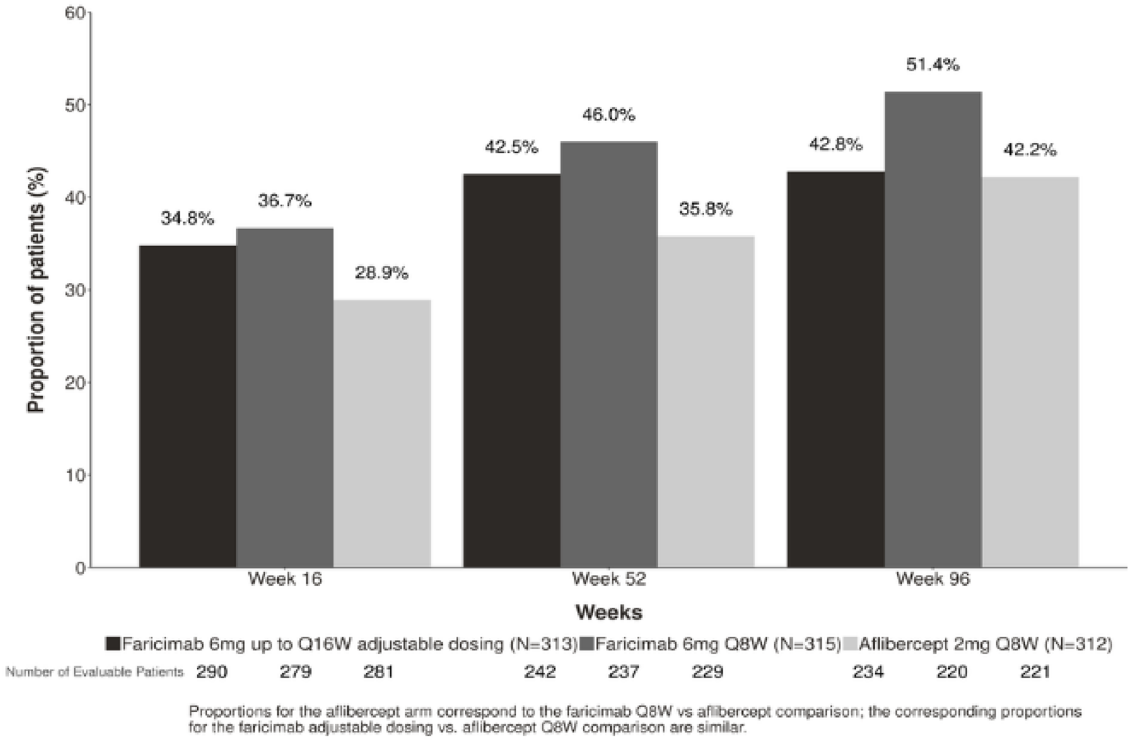
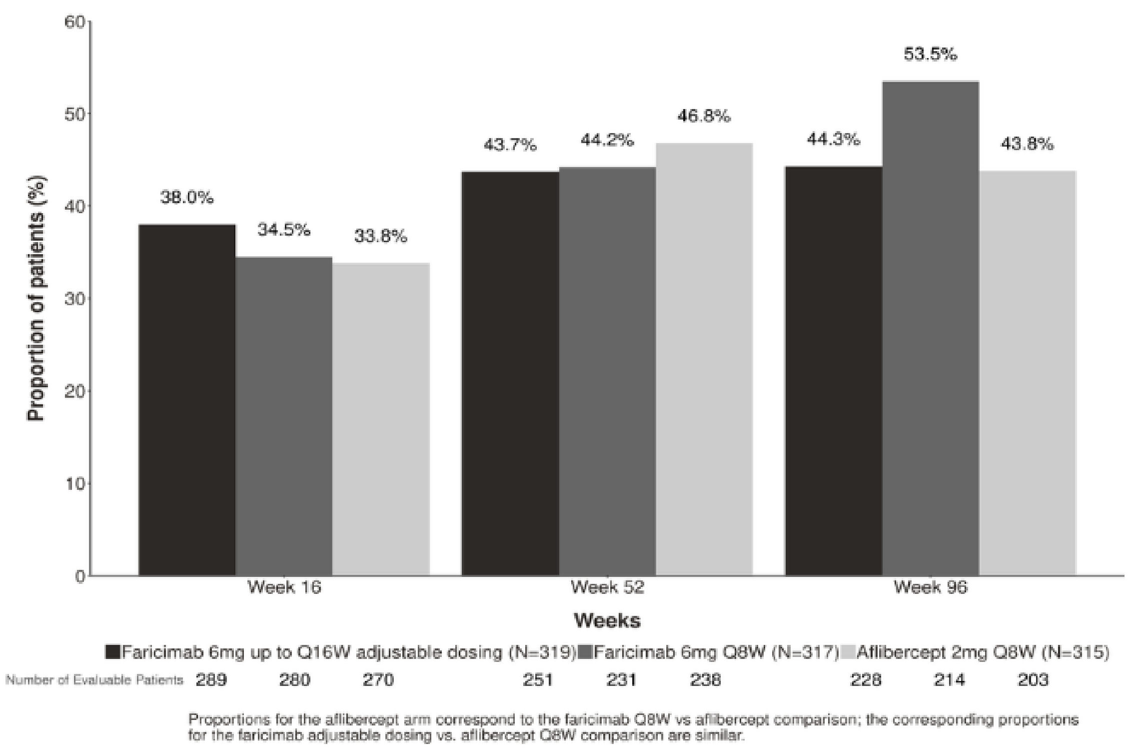


Figure 6: Proportion of patients who achieved ≥ 2-step improvement from baseline in ETDRS-DRSS score at week 16, week 52 and at week 96 in RHINE



The proportions of patients with new proliferative DR diagnosis (defined by ETDRS-DRSS 61 or worse) from baseline to week 96 were comparable between the VABYSMO Q8W, VABYSMO up to Q16W adjustable dosing and aflibercept Q8W dosed patients in both YOSEMITE and RHINE studies. Almost no patients required vitrectomy (0 to 4 per group) or Panretinal Photocoagulation (PRP) (1 to 2 per group) during the two-year duration of the studies.

DR treatment effects in the subgroup of patients who were anti-VEGF naive prior to study participation were comparable to those observed in the overall DR evaluable population. Treatment effects in evaluable subgroups (e.g. by age, gender, race, baseline HbA1c, and baseline visual acuity) in each study were generally consistent with the results in the overall population.

Treatment effects in subgroups by DR severity at baseline were different and showed the greatest ⩾ 2-step DRSS improvements among patients with moderately severe and severe non-proliferative DR with approximately 90% of patients achieving improvements. These results were comparable across the study arms, and comparable in overall and anti-VEGF treatment-naive populations.

Treatment of Macular Edema Secondary to RVO

The safety and efficacy of VABYSMO were assessed in two randomised, multi-centre, double-masked, 72-week long studies in patients with macular edema secondary to BRVO (BALATON) or C/HRVO (COMINO). Active comparator-controlled data are available through month 6.

A total of 1,282 patients (553 in BALATON and 729 in COMINO) were enrolled in the two studies, with 1,276 patients treated with at least one dose through week 24 (641 with VABYSMO).

In both studies, patients were randomized in a 1:1 ratio to one of two treatment arms:

- VABYSMO 6 mg Q4W for six consecutive monthly doses
- Aflibercept 2 mg Q4W for six consecutive monthly doses

After six initial monthly doses, patients initially randomized to the 2 mg aflibercept arm moved to the 6 mg VABYSMO arm, and could have received up to Q16W adjustable dosing regimen, where the dosing interval could be increased in 4-week increments up to Q16W or decreased by 4-, 8- or 12-weeks based on an automated objective assessment of pre-specified visual and anatomic disease activity criteria.

Both studies showed efficacy in the primary endpoint, defined as the change from baseline in BCVA at week 24, as measured by the ETDRS Letter Score. In both studies, VABYSMO Q4W treated patients had a non-inferior mean change from baseline in BCVA at week 24, compared to patients treated with aflibercept Q4W, and these vision gains were maintained through week 72 when patients moved to a VABYSMO up to Q16W adjustable dosing regimen.

Across studies, at week 24, patients in the VABYSMO Q4W arm showed improvement in the pre-specified efficacy endpoint of change from baseline at week 24 in the NEI VFQ-25 composite score that was comparable to aflibercept Q4W. VABYSMO Q4W also demonstrated improvements in the pre-specified efficacy endpoint of change from baseline at week 24 in the NEI VFQ-25 near activities and distance activities that were comparable to aflibercept Q4W. These results were maintained through week 72 when all patients were on VABYSMO up to Q16W adjustable dosing regimen.

Between week 24 and week 68, 81.5% and 74.0% of the patients receiving VABYSMO 6 mg up to Q16W adjustable dosing regimen achieved a Q16W or Q12W dosing interval in BALATON and COMINO, respectively. Of these patients, 72.1% and 61.6% completed at least one cycle of Q12W, and maintained Q16W or Q12W dosing interval without an interval reduction below Q12W through week 68 in BALATON and COMINO, respectively; 1.2% and 2.5% of the patients received only Q4W dosing through week 68 in BALATON and COMINO, respectively.

Detailed results of both studies are shown in Table 5, Figure 7 and Figure 8 below.

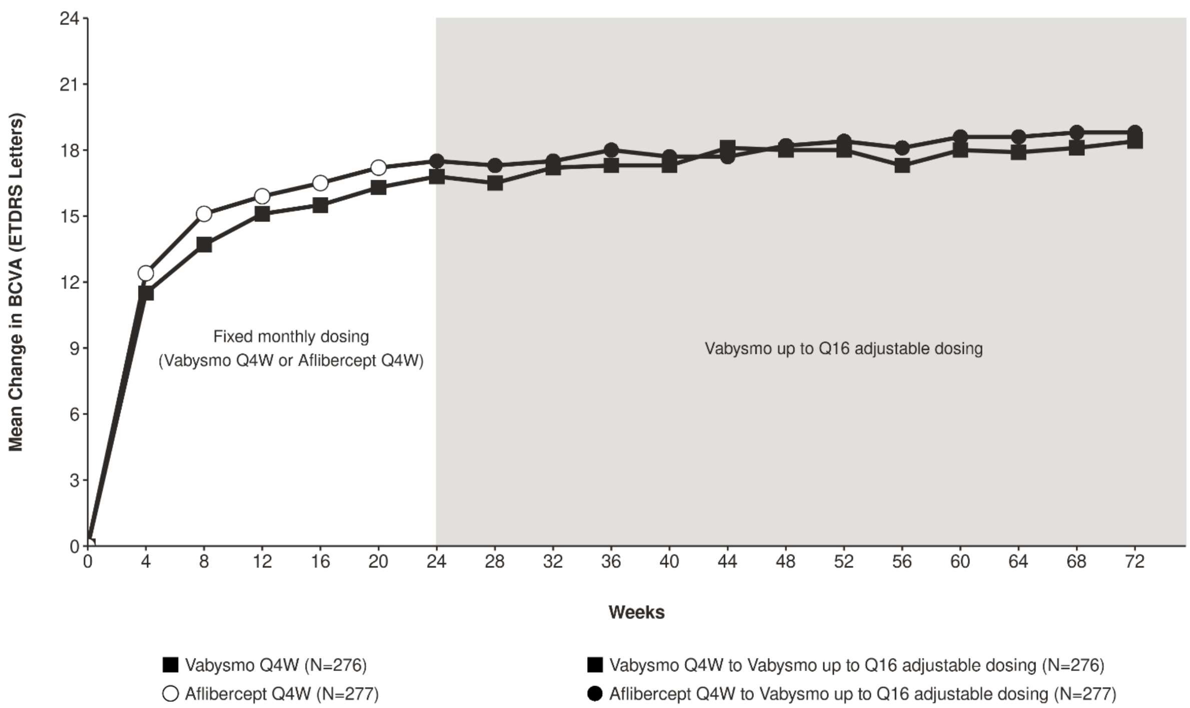
Table 5: Efficacy outcomes at the week 24 primary endpoint visits and at the end of the study in BALATON and COMINO

Efficacy Outcomes	**BALATON**				**COMINO**			
	24 Weeks		72 Weeks[a]		24 Weeks		72 Weeks[a]	
	VABYSMO N = 276	Aflibercept N = 277	VABYSMO Q4W to VABYSMO Adjustable N = 276	Aflibercept Q4W to VABYSMO Adjustable N = 277	VABYSMO N = 366	Aflibercept N = 363	VABYSMO Q4W to VABYSMO Adjustable N = 366	Aflibercept Q4W to VABYSMO Adjustable N = 363
Mean change in BCVA as measured by ETDRS letter score from baseline (95% CI)	16.9 (15.7, 18.1)	17.5 (16.3, 18.6)	18.1 (16.9, 19.4)	18.8 (17.5, 20.0)	16.9 (15.4, 18.3)	17.3 (15.9, 18.8)	16.9 (15.2, 18.6)	17.1 (15.4, 18.8)
Difference in LS mean (95% CI)	-0.6 (-2.2, 1.1)				-0.4 (-2.5, 1.6)			

Proportion of patients with ≥ 15 letter gain from baseline (CMH weighted proportion, 95% CI)	56.1% (50.4%, 61.9%)	60.4% (54.7%, 66.0%)	61.5% (56.0%, 67.0%)	65.8% (60.3%, 71.2%)	56.6% (51.7%, 61.5%)	58.1% (53.3%, 62.9%)	57.6% (52.8%, 62.5%)	59.5 (54.7%, 64.3%)
Difference in CMH weighted % (95% CI)	-4.3% (-12.3%, 3.8%)				-1.5% (-8.4%, 5.3%)			

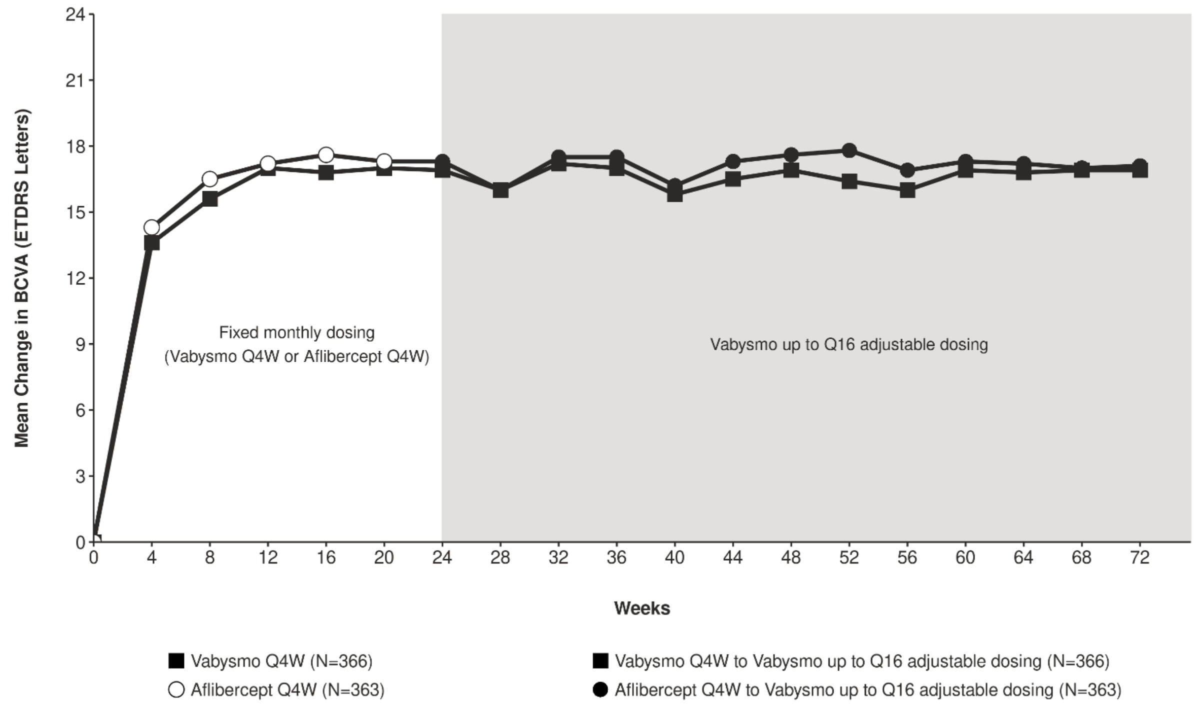
[a]Average of weeks 64, 68, 72
BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
CI: Confidence Interval
LS: Least Square
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.

Figure 7: Mean change in visual acuity from baseline to week 72 in BALATON



VABYSMO 6 mg up to Q16W adjustable dosing started at week 24 but not all patients received VABYSMO at week 24.

Figure 8: Mean change in visual acuity from baseline to week 72 in COMINO



VABYSMO 6 mg up to Q16W adjustable dosing started at week 24 but not all patients received VABYSMO at week 24.

3.1.3 Immunogenicity

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to VABYSMO with the incidence of antibodies to other products may be misleading.

In the nAMD, DME and RVO studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8%, 0.8% and 1.1%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 13.8%, 9.6% and 14.4% of patients with nAMD, DME and RVO randomized to faricimab, respectively, treated with VABYSMO across studies and across treatment groups. As with all therapeutic proteins, there is the potential for immune response to VABYSMO.

3.2 PHARMACOKINETIC PROPERTIES

Faricimab is administered intravitreally to exert local effects in the eye.

Absorption and distribution

Based on a population pharmacokinetic analysis (including nAMD and DME N = 2,246), maximum free (unbound to VEGF-A and Ang-2) faricimab plasma concentrations

(Cmax) are estimated to occur approximately 2 days post-dose. Mean (±SD [standard deviation]) plasma Cmax are estimated 0.23 (0.07) µg/mL and 0.22 (0.07) µg/mL respectively in nAMD and in DME patients. After repeated administrations, mean plasma free faricimab trough concentrations are predicted to be 0.002-0.003 µg/mL for Q8W dosing.

Faricimab exhibited dose-proportional pharmacokinetics (based on Cmax and AUC) over the dose range 0.5 mg-6 mg. No accumulation of faricimab was apparent in the vitreous or in plasma following monthly dosing.

Maximum plasma free faricimab concentrations are predicted to be approximately 600 and 6000-fold lower than in aqueous and vitreous humour respectively. Therefore, systemic pharmacodynamic effects are unlikely, further supported by the absence of significant changes in free VEGF and Ang-2 concentration in plasma upon faricimab treatment in clinical studies.

Population pharmacokinetic analysis has shown an effect of age and body weight on ocular or systemic pharmacokinetics of faricimab respectively. Both effects were considered not clinically meaningful; no dose adjustment is needed.

Biotransformation and elimination

Faricimab is a protein-based therapeutic hence its metabolism and elimination have not been fully characterised. Faricimab is expected to be catabolised in lysosomes to small peptides and amino acids, which may be excreted renally, in a similar manner to the elimination of endogenous IgG.

The faricimab plasma concentration-time profile declined in parallel with the vitreous and aqueous concentration-time profiles. The estimated mean ocular half-life and apparent systemic half-life of faricimab is approximately 7.5 days.

Pharmacokinetic analysis of patients with nAMD, DME, and RVO (N=2,977) has shown that the pharmacokinetics of faricimab are comparable in nAMD, DME, and RVO patients.

3.2.1 Pharmacokinetics in Special Populations

Pediatric Population

The safety and efficacy of VABYSMO in pediatric patients have not been established.

Geriatric Population

In the six Phase III clinical studies, approximately 58% (1,496/2,571) of patients randomised to treatment with faricimab were ⩾ 65 years of age. Population pharmacokinetic analysis has shown an effect of age on ocular pharmacokinetics of faricimab. The effect was considered not clinically meaningful. No dose adjustment is required in patients 65 years and above (see *section 2.2 Dosage and Administration*).

Renal impairment

No specific studies in patients with renal impairment have been conducted with faricimab. Pharmacokinetic analysis of patients in the four Phase III clinical studies of which 64% had renal impairment (mild 38%, moderate 24%, and severe 2%), revealed no differences with respect to systemic pharmacokinetics of faricimab after intravitreal administration of faricimab. No dose adjustment is required in patients with renal impairment (see *section 2.2 Dosage and Administration*).

Hepatic impairment

No specific studies in patients with hepatic impairment have been conducted with faricimab. However, no special considerations are needed in this population because metabolism occurs via proteolysis and does not depend on hepatic function. No dose adjustment is required in patients with hepatic impairment (see *section 2.2 Dosage and Administration*).

Other

The systemic pharmacokinetics of faricimab are not influenced by race. Gender was not shown to have a clinically relevant influence on systemic pharmacokinetics of faricimab. No dose adjustment is needed.

3.3 NONCLINICAL SAFETY

3.3.1 Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of VABYSMO.

3.3.2 Genotoxicity

No studies have been performed to establish the mutagenic potential of VABYSMO.

3.3.3 Impairment of Fertility

While the anti-VEGF and anti-Ang2 components could mean a potential theoretical mechanism-based risk to reproduction, the systemic exposure stemming from intravitreal treatment suggests that this risk may be negligible. No effects on fertility were observed in a 6-month cynomolgus monkey study with VABYSMO.

3.3.4 Reproductive Toxicity

VEGF inhibition has been shown to cause malformations, embryo-fetal resorption, and decreased fetal weight. VEGF inhibition has also been shown to affect follicular development, corpus luteum function, and fertility. No dedicated studies addressing the effects of Ang-2 inhibition on pregnancy are available. Based on non-clinical information

Ang-2 inhibition may lead to effects comparable to VEGF inhibition. Systemic exposure after ocular administration of VABYSMO is very low.

No effects on reproductive organs were observed in a 6-month cynomolgus monkey study with VABYSMO. No effects on pregnancy or fetuses were observed in an embryo-fetal development study in pregnant cynomolgus monkeys given 5 weekly IV injections of VABYSMO starting on day 20 of gestation at 1 mg/kg or 3 mg/kg. Serum exposure (Cmax) in monkeys at the no observed adverse effect level (NOAEL) dose of 3 mg/kg was more than 500 times that in humans at a dose of 6 mg given by intravitreal injection once every 4 weeks.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

VABYSMO should not be used after the expiry date (EXP) shown on the pack.

Storage: Store in a refrigerator (2°C-8°C).

Do not freeze.

Keep the vial in the original carton to protect from light.

Prior to use, the unopened vial of VABYSMO may be kept at room temperature, 20°C to 25°C (68°F to 77°F), for up to 24 hours.

Ensure that the injection is given immediately after preparation of the dose.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Preparation for Administration

VABYSMO is a sterile, preservative-free, clear to opalescent, colorless to brownish-yellow solution.

Do not shake.

VABYSMO should be inspected visually upon removal from the refrigerator and prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

The contents of the vial and transfer filter needle are sterile and for single use only. Do not use if the packaging, vial and/or transfer filter needle are damaged or expired.

Use aseptic technique for preparation of the intravitreal injection.

Instructions for administration

See section *2.2 Dosage and Administratio*n for dosing instructions.

For detailed instructions on administration, refer to the Instructions for Use.

Packs

Each box contains 1 vial of VABYSMO 6mg/0.05mL and 1 filter needle.

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Medicine: keep out of reach of children

MYVabysmo20250218CDS6.1

Revision date: Feb 2025

Drug Product Manufacturing and Batch Release Site:

F. Hoffmann-La Roche Ltd Wurmisweg CH-4303 Kaiseraugst Switzerland.

INSTRUCTION FOR USE – PREPARATION FOR ADMINISTRATION

Before you start:

- Read all the instructions carefully before using VABYSMO.
- The VABYSMO kit includes a glass vial and transfer filter needle. The glass vial is for a single dose only. The filter needle is for single use only.
- VABYSMO should be stored refrigerated at temperatures between 2ºC to 8ºC (36ºF to 46ºF).

    Do not freeze.

    Do not shake.

- Allow VABYSMO to reach room temperature, 20°C to 25°C (68°F to 77°F) before proceeding with the administration. Keep the vial in the original carton to protect from light.
- The VABYSMO vial may be kept at room temperature for up to 24 hours.
- The VABYSMO vial should be inspected visually prior to administration.
- The VABYSMO is a clear to opalescent and colorless to brownish-yellow liquid solution.

    Do not use if particulates, cloudiness, or discoloration are visible.

    Do not use if the packaging, vial and/or transfer filter needle are expired, damaged, or have been tampered with (see **Figure A**).

- Use aseptic technique to carry out the preparation of the intravitreal injection.

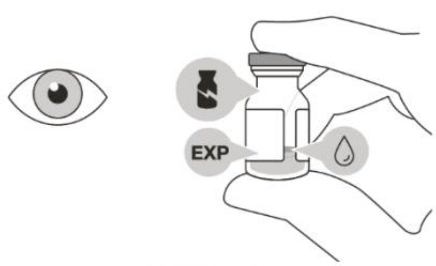


Figure A

1. Gather the following supplies:

- One VABYSMO vial (included)
- One sterile 5-micron blunt transfer filter needle 18-gauge x 1½ inch (included)
- One sterile 1 mL Luer lock syringe with a 0.05 mL dose mark (**not included**)
- One sterile injection needle 30-gauge x ½ inch (**not included**)

  Note that a 30-gauge injection needle is recommended to avoid increased injection forces that could be experienced with smaller diameter needles.

- Alcohol swab (not included).

---

2. To ensure all liquid settles at the bottom of the vial, place the vial upright on a flat surface (for about 1 minute) after removal from packaging (see **Figure B**). Gently tap the vial with your finger (see **Figure C**), as liquid may stick to the top of the vial.


Figure B

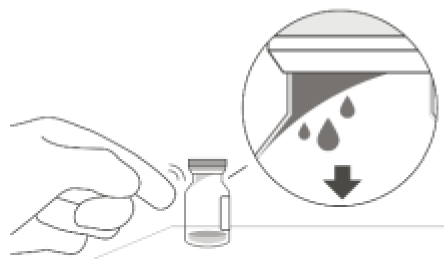


Figure C

---

3. Remove the flip-off cap from the vial (see **Figure D**) and wipe the vial septum with an alcohol swab (see **Figure E**).

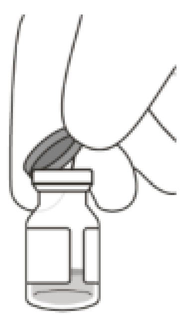


Figure D

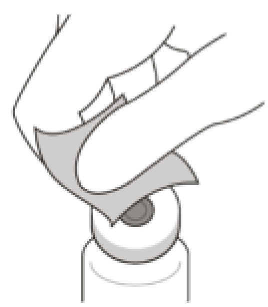


Figure E

---

4. Aseptically and firmly attach the included 18-gauge x 1½ inch transfer filter needle onto a 1 mL Luer lock syringe (see **Figure F**).

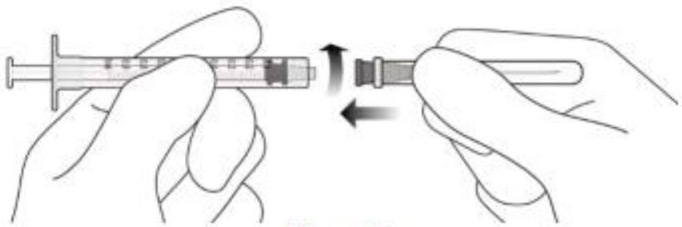


Figure F

5. Using aseptic technique, push the transfer filter needle into the center of the vial septum (see **Figure G**), push it all the way in, then tilt the vial slightly so that the needle touches the bottom edge of the vial (see **Figure H**).

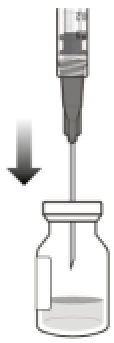


Figure G

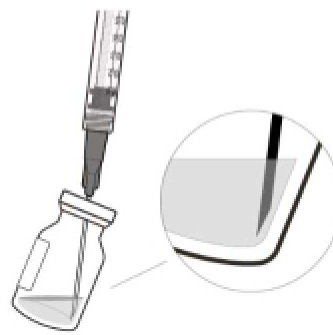


Figure H

6. Hold the vial slightly inclined and **slowly** withdraw all the liquid from the vial (see **Figure I**). Keep the bevel of the transfer filter needle submerged in the liquid, to avoid introduction of air.

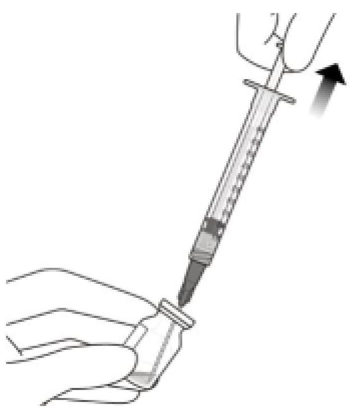


Figure I

7. Ensure that the plunger rod is drawn sufficiently back when emptying the vial, in order to completely empty the transfer filter needle (see **Figure I**).

8. Disconnect the transfer filter needle from the syringe and dispose of it in accordance with local regulations.

Do not use the transfer filter needle for the intravitreal injection.

9. Aseptically and firmly attach a 30-gauge x ½ inch injection needle onto the Luer lock syringe (see **Figure J**).

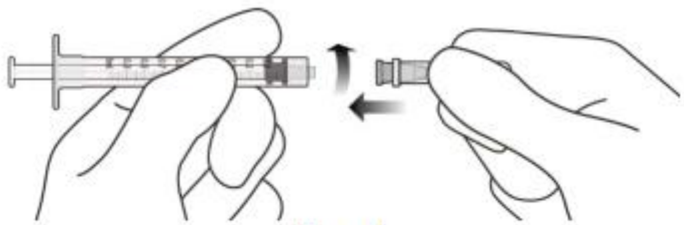


Figure J

10. Carefully remove the plastic needle shield from the needle by pulling it straight off.

11. To check for air bubbles, hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see **Figure K**).

Figure K

12. Carefully expel the air from the syringe and needle, and slowly depress the plunger to align the rubber stopper tip to the 0.05 mL dose mark. The syringe is ready for the injection (see **Figure L**). Ensure that the injection is given immediately after preparation of the dose.

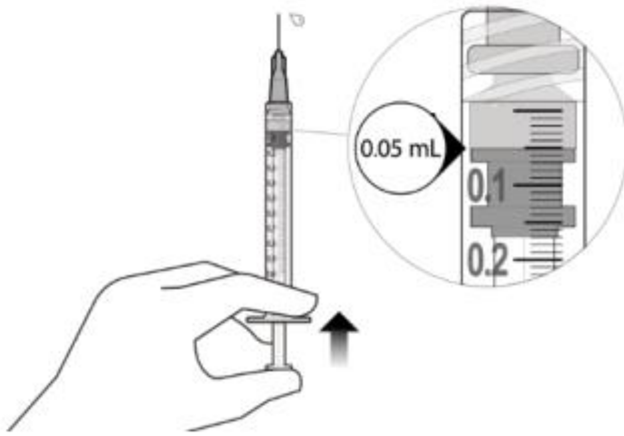


Figure L

INSTRUCTION FOR USE – INJECTION PROCEDURE

Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.05 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Any waste material or unused medicinal product should be disposed of in accordance with local regulations.

TEC-0200040 Version 3.0, 15-Nov-2021