PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF MEDICINE

Vabysmo® 6 mg (0.05 mL of 120 mg/ mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Faricimab

Each vial contains 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.

Excipients with known effect: D-sucrose.

Contains D-sucrose 2.74 mg (see section 4.4 Special warnings and precautions for use).

For the full list of excipients,(see section 6. 1 List of excipients)

3. PHARMACEUTICAL FORM

Solution for injection

Clear to opalescent, colourless to brownish-yellow solution, in a single-dose glass vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Vabysmo is a bispecific angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

- neovascular (wet) age-related macular degeneration (nAMD) (see section 5.1 Pharmacodynamic properties).
- diabetic macular oedema (DME) (see section 5.1).

4.2 Posology and method of administration

General

For intravitreal injection only. Vabysmo must be administered by a qualified physician experienced in intravitreal injections. Each vial should only be used for the treatment of a single eye.

Neovascular (wet) age-related macular degeneration (nAMD)

The recommended dose for Vabysmo is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 4 doses, followed by 6 mg (0.05 mL) via intravitreal injection at a dosing interval of up to every 16 weeks (4 months). Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion.

Diabetic macular edema (DME)

The recommended dose for Vabysmo is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 4 doses, followed by 6 mg (0.05 mL) via intravitreal injection at intervals of up to every 16 weeks (4 months). Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion.

Method of administration

Vabysmo should be inspected visually for particulate matter and discoloration prior to administration.

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.

Comprehensive instructions for the administration of Vabysmo are given in the Instructions for Use.

Duration of treatment

Vabysmo is intended for long-term treatment.

Delayed or missed dose

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.

If visual and/or anatomic outcomes indicate that the patient is not benefitting from continued treatment, Vabysmo should be discontinued.

Dose Modifications

No dose modifications of Vabysmo are recommended.

Special populations

Paediatric population

The safety and efficacy of Vabysmo in children and adolescents have not been established.

Elderly use

In the four Phase III clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with Vabysmo were ≥ 65 years of age. Population pharmacokinetic analysis has shown an effect of age on ocular pharmacokinetics of faricimab. No dose adjustment is required in patients ≥ 65 years of age (see section 4.7 Effects on ability to drive and use machines and 5.2 Pharmacokinetics properties).

Renal impairment

No specific studies in patients with renal impairment have been conducted with Vabysmo. Pharmacokinetic analysis of patients in all 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 Vabysmo.
No dose adjustment is required in patients with renal impairment. (see section 5.2 Pharmacokinetics properties).

Hepatic impairment

No specific studies in patients with hepatic impairment have been conducted with Vabysmo. 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 5.2 Pharmacokinetics properties).

Other Special Patient Populations

No special dosage modification is required for any of the populations that have been studied (e.g., elderly, gender, race).

4.3 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 listed in section 6.1.Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

4.4 Special warnings and precautions for use

General

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

Sugar

Vabysmo contains D sucrose. Patients with the rare hereditary conditions of galactose intolerance lactase deficiency, glucose-galactose malabsorption intolerance should not take Vabysmo. Vabysmo contains D sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Intravitreal injection-related reactions

Intravitreal injections, including those with Vabysmo have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment and retinal tear and iatrogenic traumatic cataract. (see section 4.8 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 events without delay, to permit prompt and appropriate management.

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including those with Vabysmo. 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 and/or vision 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.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with Vabysmo (see section 4.8 Undesirable effects). 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.

Bilateral Treatment

The safety and efficacy of Vabysmo administered in both eyes concurrently have not been studied.

Concomitant use of other anti-VEGF

There are no data available on the concomitant use of Vabysmo with anti-VEGF medicinal products in the same eye.

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.
- 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

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 Vabysmo therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Populations with limited data

There is only limited experience in the treatment of DME patients with HbA1c over 10%, patients with high-risk proliferative diabetic retinopathy (DR), or nAMD and DME patients with active systemic infections. There is also no experience of treatment with Vabysmo in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

4.5 Interaction with other medicines and other forms of interaction

No drug-drug interaction studies have been performed with Vabysmo.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are no data from the use of Vabysmo in pregnant women.

No adverse effects were observed in a study in pregnant cynomologus monkeys given Vabysmo intravenously throughout the period of organogenesis at doses achieving more than 500 times the predicted systemic human exposure of Vabysmo after treatment of a single eye (see section 5.2 Pharmacokinetic properties).

It is not known whether Vabysmo can cross the placenta or cause harm to the fetus when administered to pregnant women. 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. Although the systemic exposure after ocular administration is very low, Vabysmo should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

Labor and delivery

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

Breastfeeding

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.

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 5.3 Preclinical safety data).

Drug Abuse and Dependence

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

4.7 Effects on 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

Pediatric Use

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

Elderly Use

In the four Phase III clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with Vabsmo were ≥ 65, years of age. No significant differences in efficacy or safety of Vabysmo were seen with increasing age in these studies (see section 4.2 Posology and method of administration and 5.2 Pharmacokinetics properties)

Renal Impairment

No dose adjustment is required in patients with renal impairment (see section 4.2 Posology and method of administration and 5.2 Pharmacokinetics properties).

Hepatic Impairment

The safety and efficacy of Vabysmo in patients with hepatic impairment has not been studies (see section 4.2 Posology and method of administration and 5.2 Pharmacokinetics properties).

4.8 Undesirable effects

Clinical Trials

Summary of safety profile

A total of 3,213 patients constituted the safety population in the four Phase III clinical studies for two years (1,926 Vabysmo treated patients; 664 in nAMD and 1,262 in DME).

The most serious adverse reactions were endophthalmitis (0.5%), rhegmatogenous retinal detachment (< 0.1%), retinal tear (0.2%), vitritis (0.3%) and uveitis (0.6%) and traumatic cataract (< 0.1%) .

The most frequently reported adverse reactions in patients treated with Vabysmo were cataract (13%), conjunctival hemorrhage (8 % vitreous detachment (5%), retinal pigment epithelial tear (nAMD only) (3%), IOP increased (4%) and eye pain (3%).

Tabulated list of adverse reactions

The safety data described below include all adverse reactions from the pooled data across four Phase III clinical studies in the indications nAMD and DME, 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	**Frequency category**
Eye disorders	
Cataract	Very Common
Conjunctival haemorrhage	Common
Vitreous detachment	Common
Vitreous floaters	Common
Retinal pigment epithelial tear (nAMD only)	Common
Intraocular pressure increased	Common
Eye pain	Common
Eye irritation	Uncommon
Vitreous haemorrhage	Uncommon
Ocular discomfort	Uncommon
Lacrimation increased	Uncommon
Eye pruritus	Uncommon

Corneal abrasion	Uncommon
Ocular hyperaemia	Uncommon
Vision blurred	Uncommon
Iritis	Uncommon
Uveitis	Uncommon
Iridocyclitis	Uncommon
Vitritis	Uncommon
Conjunctival hyperamia	Uncommon
Sensation of foreign body	Uncommon
Endophthalmitis	Uncommon
Procedural pain	Uncommon
Retinal tear	Uncommon
Rhegmatogenous retinal detachment	Uncommon
Visual acuity reduced transiently	Rare
Traumatic cataract	Rare

Description of selected adverse reactions

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 and DME. Across indications no notable difference between the groups treated with Vabysmo and the comparator were observed.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Report Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, other ocular vascular disorder agents, ATC code: S01LA09.

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 destabilisation, 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 destabilisation. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularisation.
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 four Phase III studies.
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 -131µm 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 an 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 mm2 and 0.4 mm2 in Vabysmo vs. 0.4 mm2 and 1.0 mm2 in aflibercept, in TENAYA and LUCERNE, respectively). There was a comparable reduction in CNV leakage area from baseline across treatment arms (-3.8 mm2 and -3.2 mm2 in Vabysmo and -3.0 mm2and -2.2 mm2 in aflibercept, in TENAYA and LUCERNE, respectively).

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.

Clinical / Efficacy Studies

Treatment of nAMD

The safety and efficacy of Vabysmo were assessed in two randomized, multi-centre, double-masked, active comparator-controlled, 2-year studies in patients with nAMD, TENAYA and LUCERNE. 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 years 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 proportion,95% CI)	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%)
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 bAverage 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

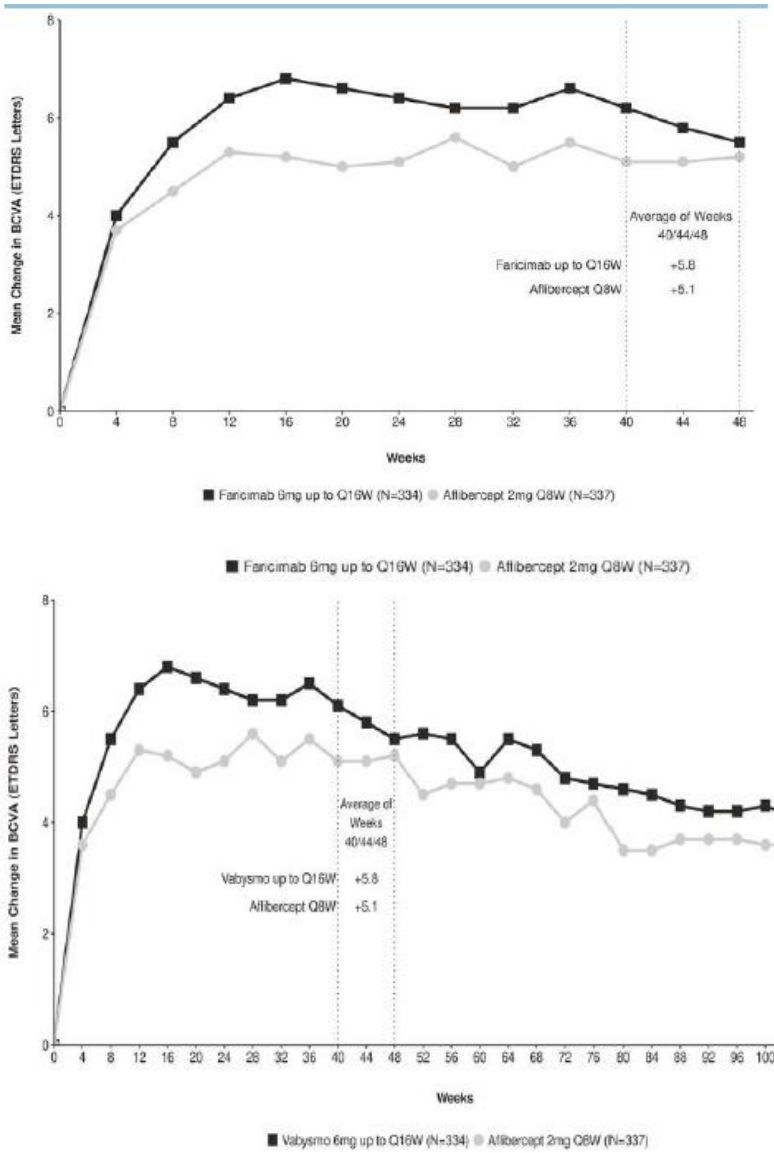
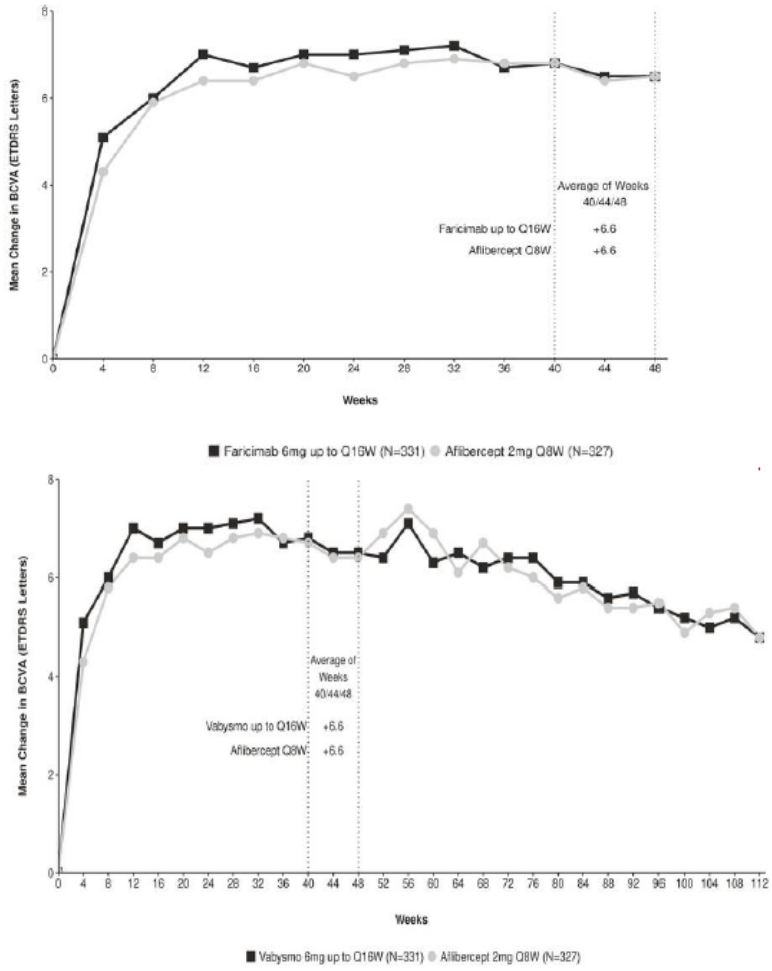


Figure 2: Mean change in visual acuity from baseline to week 112 in LUCERNE



In both TENAYA and LUCERNE, improvements from baseline 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~~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) 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 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 = 262	VABYSMO up to Q16W adjustable dosing N = 270	Aflibercept Q8W N = 259	VABYSMO Q8W N = 317	VABYSMO up to Q16W adjustable dosing N = 319	Aflibercept Q8W N = 315	VABYSMO Q8W N = 259	VABYSMO up to Q16W adjustable dosing N = 282	Aflibercept Q8W N = 254
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

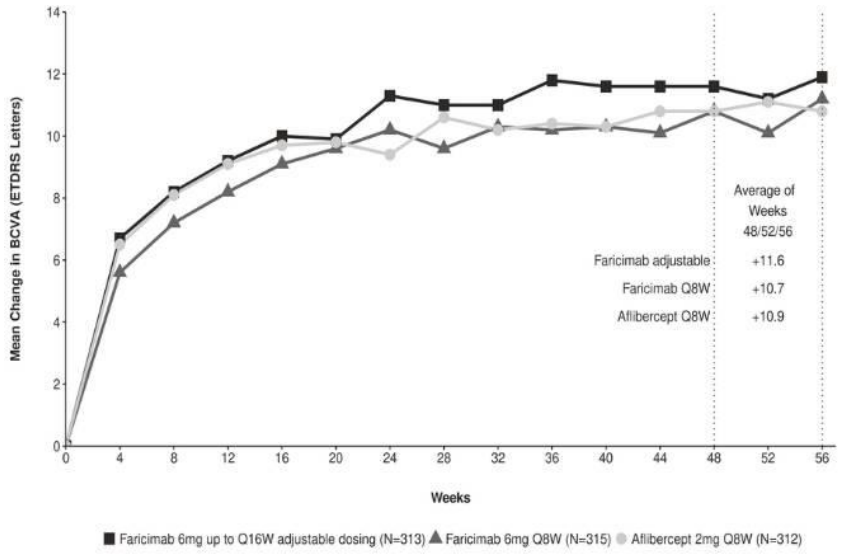
CI: Confidence Interval

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



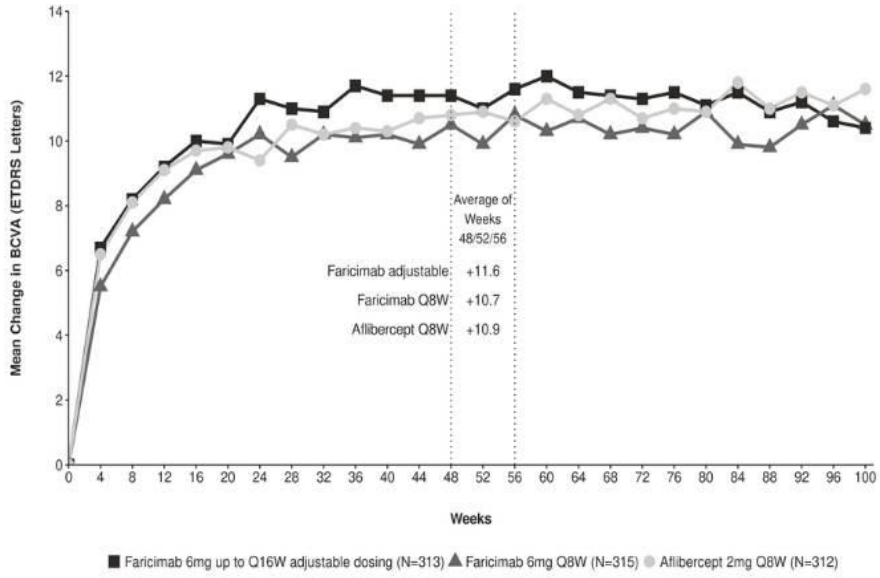
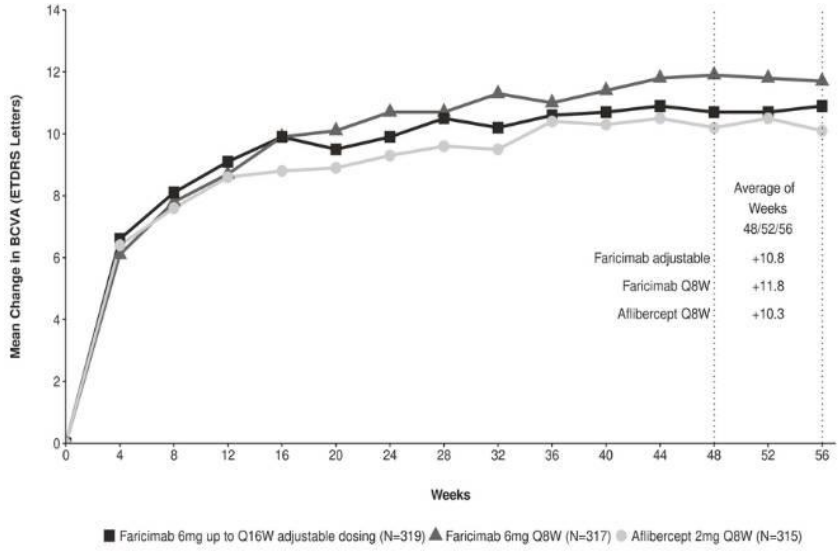


Figure 4: Mean change in visual acuity from baseline to year 2 (week 100~~56~~) in RHINE



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 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-point 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 ~~and~~ 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)

Efficacy Outcomes	**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, 95% CI year 2)	10.2 % (1.6 %, 18.7 %)	6.1% (-2.4%, 14.6 %)		9.1% (0.0%, 18.2%)	0.0% (-8.9%, 8.9%)		-2.6% (-11.3 %,	-3.5% (-12.1 %,		9.7% (0.4%, 19.1%)	0.3% (-8.9%, 9.5%)	

							6.2%)	5.1%)				
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%)	

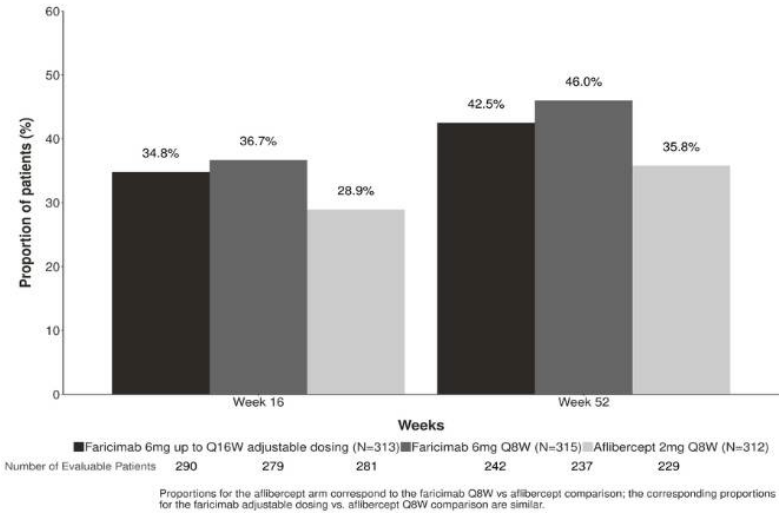
ETDRS-DRSS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale

CI: Confidence Interval

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 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



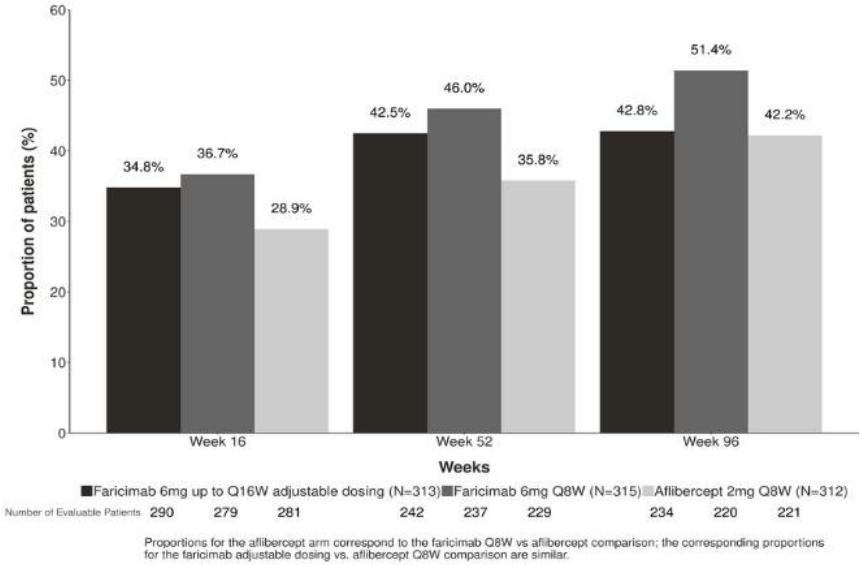
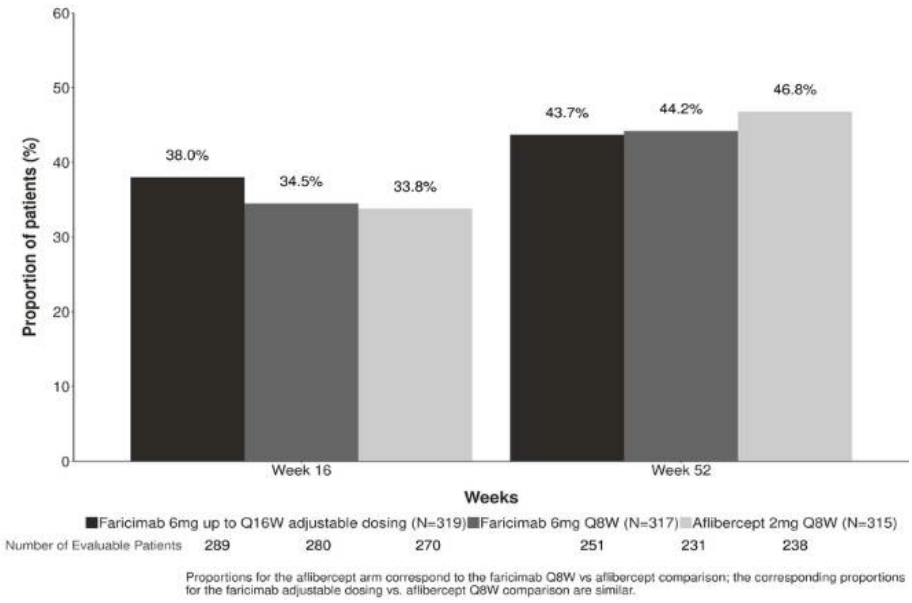
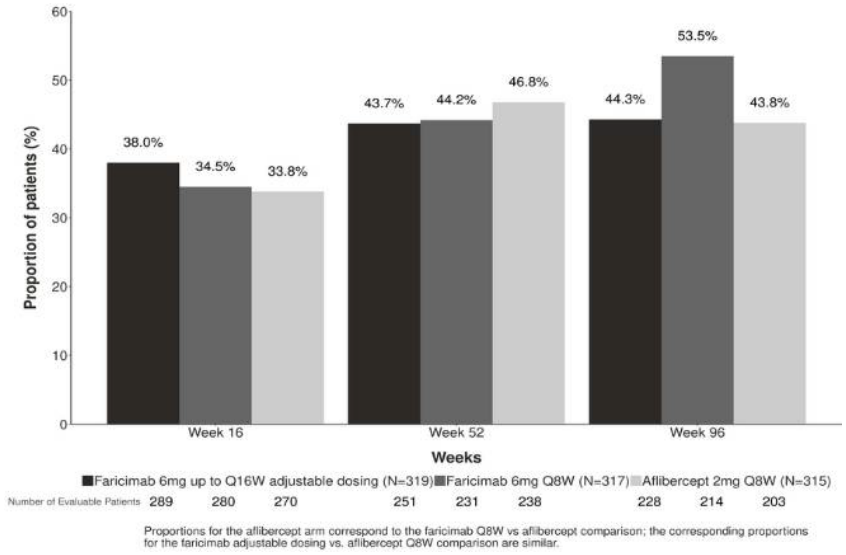


Figure 6. Proportion of patients who achieved ≥ 2-step improvement from baseline in ETDRS-DRSS score at week 16, week 52 and at week 96 in RHINE





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.

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

5.2 Pharmacokinetic properties

Absorption

Vabysmo is administered intravitreally (IVT) to exert local effects in the eye. There have been no clinical studies performed with other routes of administration.

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

Distribution

Maximum plasma free faricimab concentrations are predicted to be approximately 600 and 6000-fold lower than in aqueous and vitreous humour respectively and below the binding affinity for VEGF and Ang-2. 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.

Metabolism

The metabolism of faricimab has not been directly studied, as monoclonal antibodies are cleared principally by catabolism.

Elimination

The estimated mean apparent systemic half-life of faricimab is 7.5 days after IVT administration

Special populations

Pediatric Population

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

Elderly

In the four Phase III clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with Vabysmo 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.

Renal impairment

No formal pharmacokinetic study has been conducted in patients with renal impairment.

Hepatic impairment

No formal pharmacokinetic study has been conducted in patients with hepatic impairment

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.

5.3 Non-clinical safety

Carcinogenicity

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

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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine

Acetic acid 30% (for pH adjustment)

L-methionine

Polysorbate 20

Sodium chloride

D-Sucrose

Water for injections

Contains sugar (D-sucrose)

6.2 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.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store Vabysmo in the refrigerator between 2°C to 8°C.

Do not freeze.

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

Prior to use, the unopened vial may be kept at room temperature, 20°C to 25°C, for up to 24 hours.

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

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

6.5 Nature and contents of container

0.24 mL sterile, preservative-free solution in a glass vial with a coated rubber stopper sealed with an aluminium cap with a yellow plastic flip-off disk.

Pack size of 1 vial and 1 blunt transfer filter needle (18-gauge x 1½ inch, 1.2 mm x 40 mm).

6.6 Special precautions for disposal and other handling

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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley,

Midrand, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

Vabysmo 6 mg (0.05 mL of 120 mg/ mL): 56/30.1/0530

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 56/30.1/0530

10. DATE OF REVISION OF THE TEXT

Last revision: 23 August 2024

Approved Manufacturer(s):

F. Hoffmann-La Roche Ltd

Wurmisweg, 4303 Kaiseraugst

Switzerland