1. NAME OF THE MEDICINAL PRODUCT

VABYSMO 120 mg/mL (6 mg/ 0.05 mL) solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient(s): faricimab

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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)
- Diabetic macular edema (DME)

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 Dosage Instructions

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

Geriatric 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. No significant differences in efficacy or safety of VABYSMO were seen with increasing age in these studies. No dose adjustment is required in patients ≥ 65 years of age (see sections 4.4.4 Geriatric Use and 5.2 Pharmacokinetic properties, Pharmacokinetics in Special Populations).

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.

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.

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. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

4.4 Special warnings and precautions for use

4.4.1 General

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

Intravitreal injection-related reactions
Intravitreal injections, including those with VABYSMO have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment and retinal tear. 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 VEGF inhibitors and there is a theoretical risk that these may be related to VEGF inhibition.

Immunogenicity
As with all therapeutic proteins, there is the potential for immune response to VABYSMO. Patients should be instructed to report 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.

4.4.2 Drug Abuse and Dependence
There is no evidence that VABYSMO has the potential for drug abuse and dependence

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

4.4.4 Geriatric 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. No significant differences in efficacy or safety of VABYSMO were seen with increasing age in these studies (see sections 4.2 Posology and method of administration, Special Dosage Instructions and 5.2 Pharmacokinetic properties, Pharmacokinetics in Special Populations).

4.4.5 Renal Impairment.
No dose adjustment is required in patients with renal impairment (see sections 4.2 Posology and method of administration, Special Dosage Instructions and 5.2 Pharmacokinetic properties, Pharmacokinetics in Special Populations).

4.4.6 Hepatic Impairment
The safety and efficacy of VABYSMO in patients with hepatic impairment has not been studied (see sections 4.2 Posology and method of administration, Special Dosage Instructions and 5.2 Pharmacokinetic properties, Pharmacokinetics in Special Populations).

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

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, 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.

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 5.3 Preclinical safety data, Reproductive Toxicity).
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.

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.

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.

4.8 Undesirable effects

Clinical Trials

Summary of the safety profile
A total of 3,213 patients constituted the safety population in the four Phase III clinical studies (1,926 VABYSMO treated patients; 664 in nAMD and 1,262 in DME).
The most serious adverse reactions were endophthalmitis (0.2%), rhegmatogenous retinal detachment (< 0.1%), retinal tear (0.1%), vitritis (0.4%) and uveitis (0.4%) .
The most frequently reported adverse reactions in patients treated with VABYSMO were conjunctival hemorrhage (7%), vitreous floaters (3%), retinal pigment epithelial tear (3%), IOP increased (3%) and eye pain (2%).

Tabulated summary of adverse drug reactions from clinical trials

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	VABYSMO N = 1,926	Frequency category
Eye Disorders		
Conjunctival hemorrhage	6.7%	Common
Vitreous floaters	3.3%	Common
RPE tear (nAMD only)	2.9%	Common
Intraocular pressure increased	2.8%	Common
Eye pain	2.3%	Common
Eye irritation	0.9%	Uncommon
Vitreous hemorrhage	0.8%	Uncommon
Ocular discomfort	0.8%	Uncommon
Lacrimation increased	0.7%	Uncommon
Eye pruritus	0.7%	Uncommon
Corneal abrasion	0.6%	Uncommon
Ocular hyperemia	0.6%	Uncommon
Vision blurred	0.6%	Uncommon
Iritis	0.4%	Uncommon
Uveitis	0.4%	Uncommon
Iridocyclitis	0.4%	Uncommon
Vitritis	0.4%	Uncommon
Sensation of foreign body	0.4%	Uncommon
Endophthalmitis	0.2%	Uncommon
Visual acuity reduced transiently	0.2%	Uncommon
Retinal tear	0.1%	Uncommon
Rhegmatogenous retinal detachment	< 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 and DME. Across indications no notable difference between the groups treated with VABYSMO and the

comparator were observed.

Postmarketing Experience

Not applicable

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: Not yet assigned

Mechanism of action

Faricimab is a humanized bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralization of both 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.

Pharmacodynamic effects

A decrease from baseline of ocular free Ang-2 and free VEGF-A concentrations was observed from day 7 onwards throughout the treatment interval (in most patients) in the four Phase III clinical 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 -131 µm with aflibercept, in TENAYA and LUCERNE, respectively.

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 (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.

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 mm2 and -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 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 56 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. 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.

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.

Additional anatomic parameters were evaluated to assess disease progression or improvement based on change in macular leakage using fluorescein angiography. In both studies, a numerically greater proportions of patients in both VABYSMO groups achieved an absence of macular leakage between baseline and week 52, compared to those in the aflibercept group.

Clinical efficacy and safety

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, and 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.

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.

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%

Table 2: Efficacy outcomes at the primary endpoint visitsa in TENAYA and LUCERNE

Efficacy Outcomes	**TENAYA**		**LUCERNE**	
	VABYSMO up to Q16W N = 334	Aflibercept Q8W N = 337	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)	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)
Difference in LS mean (95% CI)	0.7 (-1.1, 2.5)		0.0 (-1.7, 1.8)	
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%)	20.2% (15.9%, 24.6%)	22.2% (17.7%, 26.8%)
Difference in CMH weighted % (95% CI)	4.3% (-1.6%, 10.1%)		-2.0% (-8.3%, 4.3%)	
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 %)	95.8% (93.6%, 98.0%)	97.3% (95.5%, 99.1%)

Difference in CMH weighted % (95% CI)	1.3% (-2.2%, 4.8%)		-1.5% (-4.4%, 1.3%)	

[a]Average of weeks 40, 44 and 48
BVCA: 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 48 in TENAYA

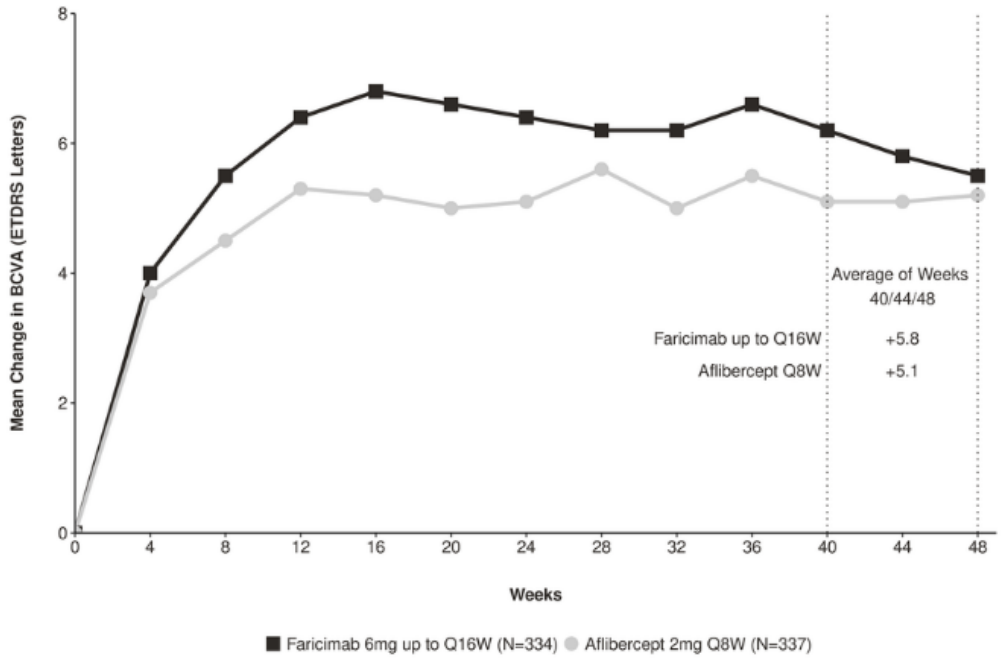
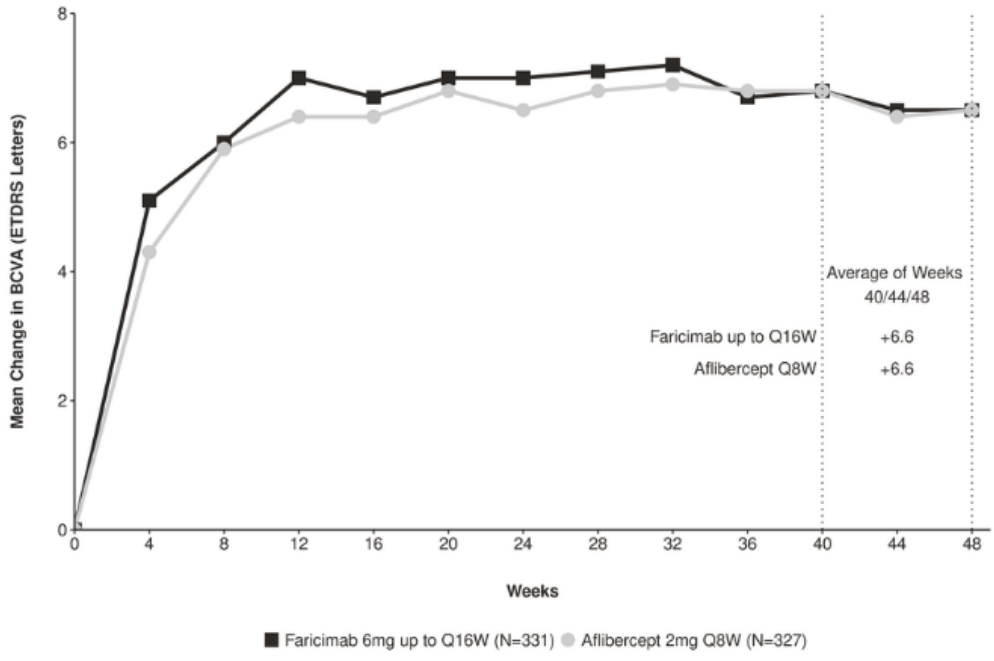


Figure 2: Mean change in visual acuity from baseline to week 48 in LUCERNE



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.

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 $\geq$ 4 point improvement from baseline in the NEI VFQ -25 composite score at week 48.

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 a total of 1,887 patients 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. Detailed results of both studies are shown in Table 3, Figure 3, and Figure 4 below.

At week 52, 74% and 71% of patients in the VABYSMO up to Q16W adjustable dosing arm achieved a Q12W or Q16W dosing interval in YOSEMITE and RHINE, respectively (53% and 51% on Q16W, 21% and 20% on Q12W).

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 primary endpoint visits[a] in YOSEMITE and RHINE

Efficacy Outcomes	YOSEMITE			RHINE		
	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
Mean change in BCVA as measured by ETDRS letter score from baseline (97.5% CI)	10.7 (9.4, 12.0)	11.6 (10.3, 12.9)	10.9 (9.6, 12.2)	11.8 (10.6, 13.0)	10.8 (9.6, 11.9)	10.3 (9.1, 11.4)
Difference in LS mean (CI)	-0.2 (-2.0, 1.6)	0.7 (-1.1, 2.5)		1.5 (-0.1, 3.2)	0.5 (-1.1, 2.1)	
Proportion of patients who gained at least 15 letters in BCVA from baseline (CMH weighted proportion, 95% CI)	29.2% (23.9%, 34.5%)	35.5% (30.1%, 40.9%)	31.8% (26.6%, 37.0%)	33.8% (28.4%, 39.2%)	28.5% (23.6%, 33.3%)	30.3% (25.0%, 35.5%)
Difference in CMH weighted % (95% CI)	-2.6% (-10.0%, 4.9%)	3.5% (-4.0%, 11.1%)		3.5% (-4.0%, 11.1%)	-2.0% (-9.1%, 5.2%)	
Proportion of patients who avoided loss of at least 15 letters in BCVA from baseline (CMH weighted proportion, 95% CI)	98.1% (96.5%, 99.7%)	98.6% (97.2%, 100.0%)	98.9% (97.6%, 100.0%)	98.9% (97.6%, 100.0%)	98.7% (97.4%, 100.0%)	98.6% (97.2%, 99.9%)
Difference in CMH weighted % (95% CI)	-0.8% (-2.8%, 1.3%)	-0.3% (-2.2%, 1.5%)		0.3% (-1.6%, 2.1%)	0.0% (-1.8%, 1.9%)	

[a]Average of weeks 48, 52, 56
BVCA: 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 1 (week 56) in YOSEMITE

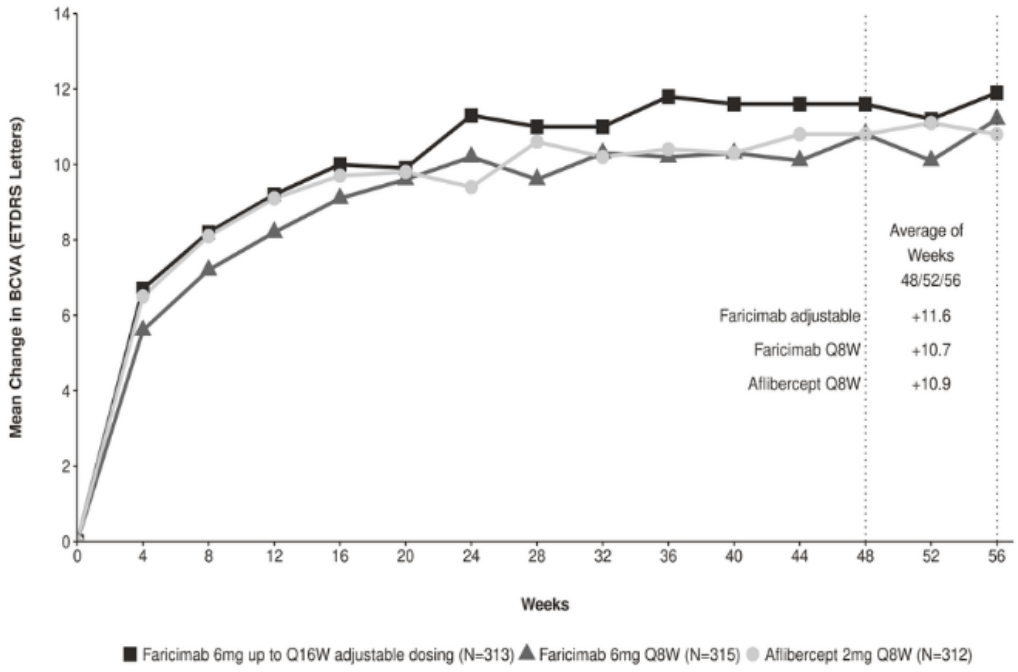
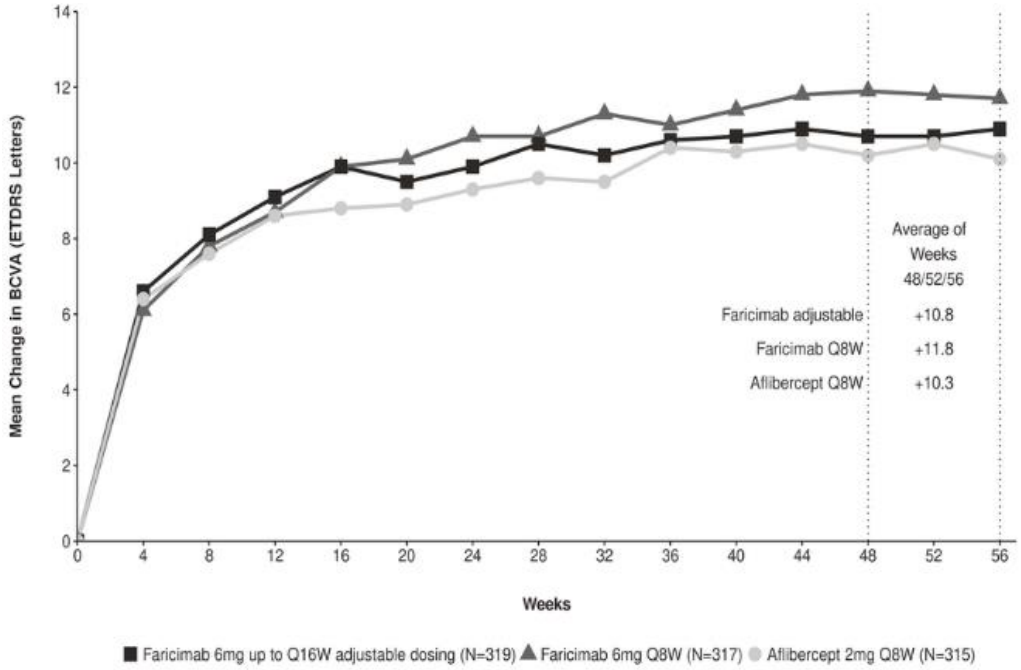


Figure 4: Mean change in visual acuity from baseline to year 1 (week 56) in RHINE



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.

In both studies, VABYSMO Q8W and up to Q16W adjustable dosing demonstrated clinically meaningful improvements from baseline to week 52 in the National Eye Institute Visual Function Questionnaire (NEI VFQ) -25 composite, near activities, distance activities, and driving scores comparable to aflibercept Q8W. Comparable proportions of patients experienced a ≥ 4 point improvement from baseline in the NEI VFQ -25 composite score at week 52 with VABYSMO Q8W, VABYSMO up to Q16W adjustable dosing, and aflibercept Q8W.

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.

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% 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.

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.

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

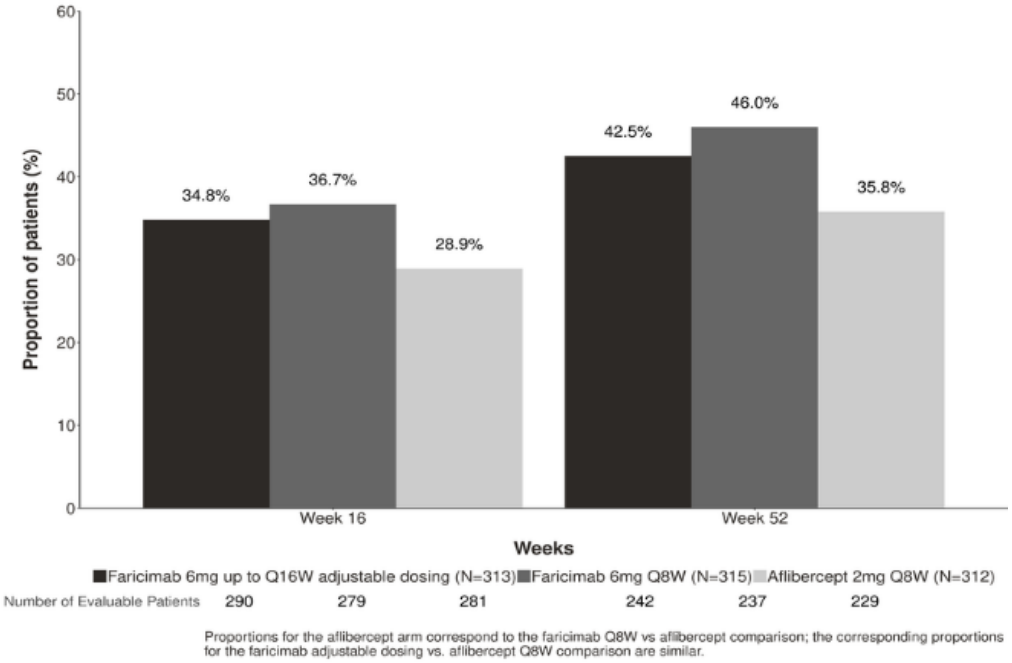
Table 4: Proportion of patients who achieved ≥ 2-step and ≥ 3-step improvement from baseline in ETDRS-DRSS score at week 52 in YOSEMITE and RHINE (DR evaluable population)

	YOSEMITE			**RHINE**		
	VABYSMO Q8W n = 237	VABYSMO up to Q16W adjustable dosing n = 242	Aflibercept Q8W n = 229	VABYSMO Q8W n = 231	VABYSMO up to Q16W adjustable dosing n = 251	Aflibercept Q8W n = 238
Proportion of patients with ≥2-step ETDRS-DRSS improvement from baseline (CMH weighted proportion)	46.0%	42.5%	35.8%	44.2%	43.7%	46.8%

Weighted Difference (97.5% CI)	10.2% (1.6%, 18.7%)	6.1% (-2.4%, 14.6%)		-2.6% (-11.3%, 6.2%)	-3.5% (-12.1%, 5.1%)	
Proportion of patients with ≥ 3-step ETDRS-DRSS improvement from baseline (CMH weighted proportion)	16.8%	15.5%	14.7%	16.7%	18.9%	19.4%
Weighted Difference (97.5% CI)	2.1% (-4.3%, 8.6%)	0.6% (-5.8%, 6.9%)		-0.2% (-5.8%, 5.3%)	-1.1% (-8.0%, 5.9%)	

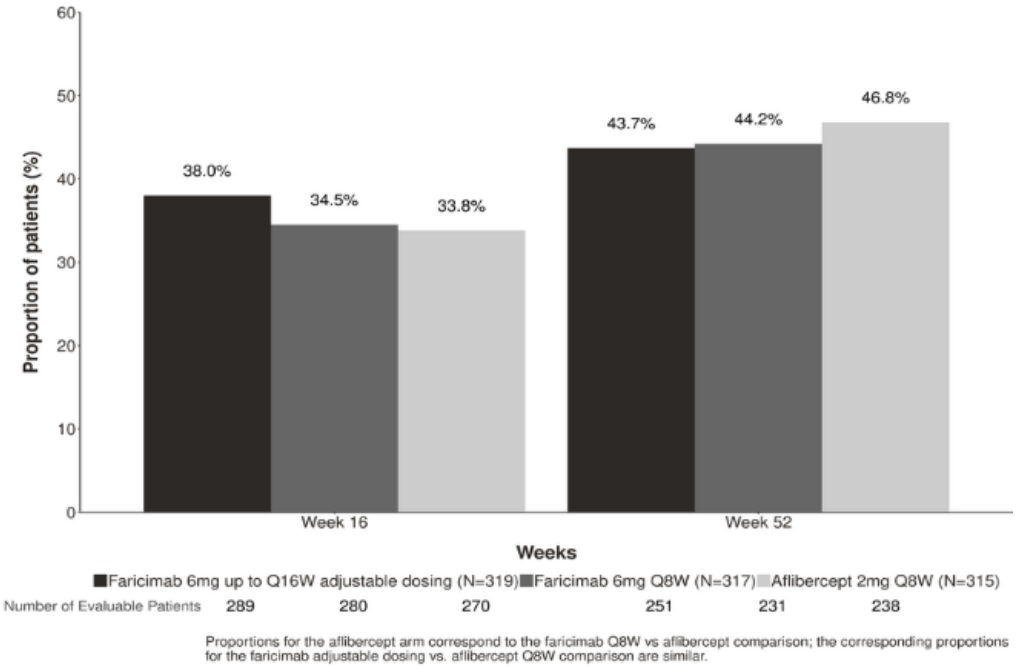
ETDRS-DRSS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.
CI: Confidence Interval
Note: CMH 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 and at week 52 in YOSEMITE



Proportions for the aflibercept arm correspond to the faricimab Q8W vs aflibercept comparison; the corresponding proportions for the faricimab adjustable dosing vs. aflibercept Q8W comparison are similar.

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



Proportions for the aflibercept arm correspond to the faricimab Q8W vs aflibercept comparison; the corresponding proportions for the faricimab adjustable dosing vs. aflibercept Q8W comparison are similar.

The proportions of patients with new proliferative DR diagnosis (defined by ETDRS-DRSS 61 or worse) from baseline to week 52 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 2 per group) or Panretinal Photocoagulation (PRP) (0 to 1 per group) during the first year 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 10.4% and 8.4% 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 and Ang-2) faricimab plasma concentrations (Cmax) are estimated to occur approximately 2 days post-dose. Mean (± SD) plasma Cmax are estimated 0.23 (0.07) µg/mL and 0.22 (0.07) µg/mL respectively in nAMD and in DME/DR 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 humor respectively and are 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 VEGFand 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.

Pharmacokinetics in special populations

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

Geriatric Population
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. No significant differences in efficacy or safety of VABYSMO were seen with increasing age in these studies.

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 VABYSMO are not influenced by race. Gender was not shown to have a clinically meaningful influence on systemic pharmacokinetics of VABYSMO.

5.3 Preclinical safety data

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.

Genotoxicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Please see on the pack.

6.4 Special precautions for storage

Store at 2°C - 8°C protected from light.

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.

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

6.5 Nature and contents of container

Type I glass vial with a fluororesin-laminated butyl rubber stopper and crimped with an aluminum seal fitted with a plastic flip-off cap.

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.

Instructions for administration
See section 4.2 Posology and method of administration.
For detailed instructions on administration, refer to the Instructions for Use.

Packs
1 vial containing solution for injection co-packaged with a transfer filter needle

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.

7. MARKETING AUTHORISATION HOLDER

Imported by Roche Thailand Ltd., Bangkok

8. DATE OF REVISION OF THE TEXT

Current at May 2021