ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vabysmo 120 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Faricimab is a humanised antibody produced in mammalian Chinese Hamster Ovary (CHO) cell culture by recombinant DNA technology.

One mL of solution contains 120 mg of 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear to opalescent, colourless to brownish-yellow solution, with a pH of 5.5 and an osmolality of 270-370 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vabysmo is indicated for the treatment of adult patients with:
- neovascular (wet) age-related macular degeneration (nAMD),
- visual impairment due to diabetic macular oedema (DME).

4.2 Posology and method of administration

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

Posology

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

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

Thereafter, an assessment of disease activity based on anatomic and/or visual outcomes is recommended 20 and/or 24 weeks after treatment initiation so that treatment can be individualised. In patients without disease activity, administration of faricimab every 16 weeks (4 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) or 12 weeks (3 months) should be considered. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reduction should be implemented if anatomic and/or

visual outcomes deteriorate (see section 5.1). There is limited safety data on treatment intervals of 8 weeks or less between injections (see section 4.4). Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion, but there is no requirement for monthly monitoring between injections.

Visual impairment due to diabetic macular oedema (DME)

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

Thereafter, treatment is individualised using a treat-and-extend approach. Based on the physician's judgement of the patient's anatomic and/or visual outcomes, the dosing interval may be extended up to every 16 weeks (4 months), in increments of up to 4 weeks. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reduction should be implemented if anatomic and/or visual outcomes deteriorate (see section 5.1). Treatment intervals shorter than 4 weeks between injections have not been studied. Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion, but there is no requirement for monthly monitoring between injections.

Duration of treatment

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

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.

Special populations

Elderly
No dose adjustment is required in patients aged 65 years or above (see section 5.2). Safety data in nAMD patients ≥ 85 years is limited (see section 4.4).

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment (see section 5.2).

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

Method of administration

For intravitreal use only.

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

The intravitreal injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, a sterile drape and a sterile eyelid speculum (or equivalent). The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section 4.8). Adequate anaesthesia and a broad-spectrum

topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

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

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

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

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

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active or suspected ocular or periocular infections.

Active intraocular inflammation.

4.4 Special warnings and precautions for use

Traceability

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

Intravitreal injection-related reactions

Intravitreal injections, including those with faricimab, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering Vabysmo. Patients should be instructed to report any symptoms, such as pain, loss of vision, photophobia, blurred vision, floaters, or redness, suggestive of endophthalmitis or any of the above-mentioned adverse reactions without delay, to permit prompt and appropriate management. Patients with increased frequency of injections may be at increased risk of procedural complications.

Intraocular pressure increases

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including those with faricimab (see section 4.8). Special precaution is needed in patients with poorly controlled glaucoma (do not inject Vabysmo while the IOP is ≥ 30 mmHg). In all cases, both the IOP and perfusion of the optic nerve head must be monitored and managed appropriately.

Systemic effects

Systemic adverse events including arterial thromboembolic events have been reported following intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors and there is a theoretical risk that these may be related to VEGF inhibition. A low incidence rate of arterial thromboembolic

events was observed in the faricimab clinical trials in patients with nAMD and DME. There are limited data on the safety of faricimab treatment in DME patients with high blood pressure (≥ 140/90 mmHg) and vascular disease, and in nAMD patients ≥ 85 years of age.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with faricimab (see section 4.8). Patients should be instructed to inform their physician of any signs or symptoms of intraocular inflammation such as vision loss, eye pain, increased sensitivity to light, floaters or worsening eye redness, which might be a clinical sign attributable to hypersensitivity against faricimab (see section 4.8).

Bilateral treatment

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

Concomitant use of other anti-VEGF

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

Withholding treatment

Treatment should be withheld in patients with:

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

Retinal pigment epithelial tear

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

Populations with limited data

There is only limited experience in the treatment of nAMD patients ≥ 85 years, and DME patients with type I diabetes, patients with HbA1c over 10%, patients with high-risk proliferative diabetic retinopathy (DR), high blood pressure (≥ 140/90 mmHg) and vascular disease, sustained dosing intervals shorter than every 8 weeks (Q8W), or nAMD and DME patients with active systemic infections. There is limited safety information on sustained dosing intervals of 8 weeks or less and

these may be associated with a higher risk of ocular and systemic adverse reactions, including serious adverse reactions. There is also no experience of treatment with faricimab in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on the biotransformation and elimination of faricimab (see section 5.2), no interactions are expected. However, faricimab should not be administered concurrently with other systemic or ocular anti-VEGF medicinal products (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment and for at least 3 months following the last intravitreal injection of faricimab.

Pregnancy

There are no or limited amount of data from the use of faricimab in pregnant women. The systemic exposure to faricimab is low after ocular administration, but due to its mechanism of action (i.e. VEGF inhibition), faricimab must be regarded as potentially teratogenic and embryo-/foetotoxic (see section 5.3).

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

Breast-feeding

It is unknown whether faricimab is excreted in human milk. A risk to the breast-fed newborn/infant cannot be excluded. Vabysmo should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from faricimab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No effects on reproductive organs or fertility were observed in a 6-month cynomolgus monkey study with faricimab (see section 5.3).

4.7 Effects on ability to drive and use machines

Vabysmo has a minor influence on the ability to drive and use machines. Temporary visual disturbances may occur 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

Summary of the safety profile

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

The most serious adverse reactions were uveitis (0.6%), endophthalmitis (0.5%), vitritis (0.3%), retinal tear (0.2%), rhegmatogenous retinal detachment (0.1%) and traumatic cataract (< 0.1%) (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions reported in clinical studies or during post-marketing surveillance 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) or not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Frequencies of adverse reactions

MedDRA System organ class	**Frequency category**
Eye disorders	
Cataract	Very common
Conjunctival haemorrhage	Common
Vitreous detachment	Common
Vitreous floaters	Common
Retinal pigment epithelial tear (nAMD only)	Common
Increased intraocular pressure	Common
Eye pain	Common
Increased lacrimation	Common
Corneal abrasion	Common
Eye irritation	Common
Vitreous haemorrhage	Uncommon
Ocular discomfort	Uncommon
Eye pruritus	Uncommon
Ocular hyperaemia	Uncommon
Blurred vision	Uncommon
Iritis	Uncommon
Uveitis	Uncommon
Iridocyclitis	Uncommon
Vitritis	Uncommon
Sensation of foreign body	Uncommon
Endophthalmitis	Uncommon
Retinal tear	Uncommon
Conjunctival hyperaemia	Uncommon
Procedural pain	Uncommon
Reduced visual acuity	Uncommon
Rhegmatogenous retinal detachment	Uncommon
Transiently reduced visual acuity	Rare
Traumatic cataract	Rare
Retinal vasculitis*	Not known
Retinal occlusive vasculitis*	Not known

Terms marked with asterisk (*) are adverse reactions which have been identified based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Description of selected adverse reactions

Retinal Vasculitis and Retinal Occlusive Vasculitis

Rare cases of retinal vasculitis and/or retinal occlusive vasculitis have been spontaneously reported in the post-marketing setting (see section 4.4). Retinal vasculitis and retinal occlusive vasculitis have also been reported in patients treated with IVT therapies.

Product-class-related 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 faricimab clinical trials in patients with nAMD and DME (see section 4.4). Across indications, no notable difference between the groups treated with faricimab and the comparator were observed.

Immunogenicity

There is a potential for an immune response in patients treated with faricimab (see section 4.4). After dosing with faricimab for up to 112 (nAMD) and 100 (DME) weeks, treatment-emergent anti-faricimab antibodies were detected in approximately 13.8% and 9.6% of patients with nAMD and DME respectively. The clinical significance of anti-faricimab antibodies on safety is unclear at this time. The incidence of intraocular inflammation in anti-faricimab antibody positive patients was 12/98 (12.2%; nAMD) and 15/128 (11.7%; DME), and in anti-faricimab antibody negative patients was 8/562 (1.4%; nAMD) and 5/1124 (0.4%; DME). The incidence of serious ocular adverse reactions in anti-faricimab antibody positive patients was 6/98 (6.1%; nAMD) and 14/128 (10.9%; DME) and in anti-faricimab antibody negative patients was 23/562 (4.1%; nAMD) and 45/1124 (4.0%; DME). Anti-faricimab antibodies were not associated with an impact on clinical efficacy or systemic pharmacokinetics.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdosing with greater than recommended injection volume may increase intraocular pressure. In the event of 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, antineovascularisation agents, ATC code: S01LA09

Mechanism of action

Faricimab is a humanised bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct pathways by neutralisation 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 sensitises 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.

Pharmacodynamic effects

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 described hereafter.

nAMD

In TENAYA and 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).

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

At week 48, in both studies there was a comparable effect of faricimab and aflibercept on the reduction of intraretinal fluid (IRF), subretinal fluid (SRF), and pigment epithelial detachment (PED). These effects in IRF, SRF, and PED were maintained at year 2. There were also comparable changes in total CNV lesion area and reductions in CNV leakage area from baseline for patients in the faricimab and aflibercept treatment arms.

DME

In YOSEMITE and RHINE, anatomic parameters related to macular oedema were part of the disease activity assessments guiding treatment decisions.

The mean CST reduction from baseline at the primary endpoint visits (averaged at weeks 48-56) was numerically greater than those observed with aflibercept, with -207 µm and -197 µm in patients treated with faricimab Q8W and faricimab 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. Consistent reductions in CST were observed through Year 2. Greater proportions of patients in both faricimab arms achieved absence of IRF and absence of DME (defined as reaching CST below 325 µm) over time through year 2 as compared to aflibercept in both studies.

Clinical efficacy and safety

nAMD

The safety and efficacy of faricimab were assessed in two randomised, multi-centre, double-masked, active comparator-controlled, 2-year non-inferiority studies in patients with nAMD, TENAYA and LUCERNE. A total of 1,329 patients were enrolled, with 1,135 (85%) patients completing the studies through week 112. A total of 1,326 patients received at least one dose (664 with faricimab). Patient ages ranged from 50 to 99 years with a mean [standard deviation; SD] of 75.9 [8.6] years.

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

- Faricimab 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 randomised to the faricimab arm received Q16W, every 12 weeks (Q12W) or Q8W dosing based on an assessment of disease activity at weeks 20 and 24. Disease activity was assessed using objective pre-specified visual (BCVA) and anatomic (CST) criteria, as well as treating physician clinical assessment of the presence of macular haemorrhage or nAMD disease activity requiring treatment (week 24 only). Patients remained on these fixed dosing intervals until week 60 without supplemental therapy. From week 60 onwards, patients in the faricimab arm moved to an adjustable dosing regimen, where their treatment interval could be modified by up to 4 week interval extensions (up to Q16W) or reduced by up to 8 week intervals (up to Q8W) based on an automated objective assessment of pre-specified visual (BCVA) and anatomic (CST and macular haemorrhage) disease activity criteria. Patients in the aflibercept arm remained on Q8W dosing throughout the study period. Both studies were 112 weeks in duration.

Results

Both studies showed efficacy in the primary endpoint, defined as the mean change from baseline in BCVA when averaged over the week 40, 44, and 48 visits and measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score (Table 2 and Table 3.). In both studies, faricimab up to Q16W treated patients had a non-inferior mean change from baseline in BCVA, as the patients treated with aflibercept Q8W at year 1, and these vision gains were maintained through week 112. Improvements from baseline BCVA at week 112 are shown in Figure 1.

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

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

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

Efficacy Outcomes	**TENAYA**			
	Year 1		**Year 2**	
	Faricimab up to Q16W N = 334	Aflibercept Q8W N = 337	Faricimab up to Q16W N = 334	Aflibercept Q8W N = 337
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)
Difference in LS mean (95% CI)	0.7 (-1.1, 2.5)		0.4 (-1.9, 2.8)	
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%)	22.5% (17.8%, 27.2%)	16.9% (12.7%, 21.1%)
Difference in CMH weighted % (95% CI)	4.3% (-1.6%, 10.1%)		5.6% (-0.7%,11.9%)	
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%)
Difference in CMH weighted % (95% CI)	1.3% (-2.2%, 4.8%)		3.4% (-1.2%, 8.1%)	

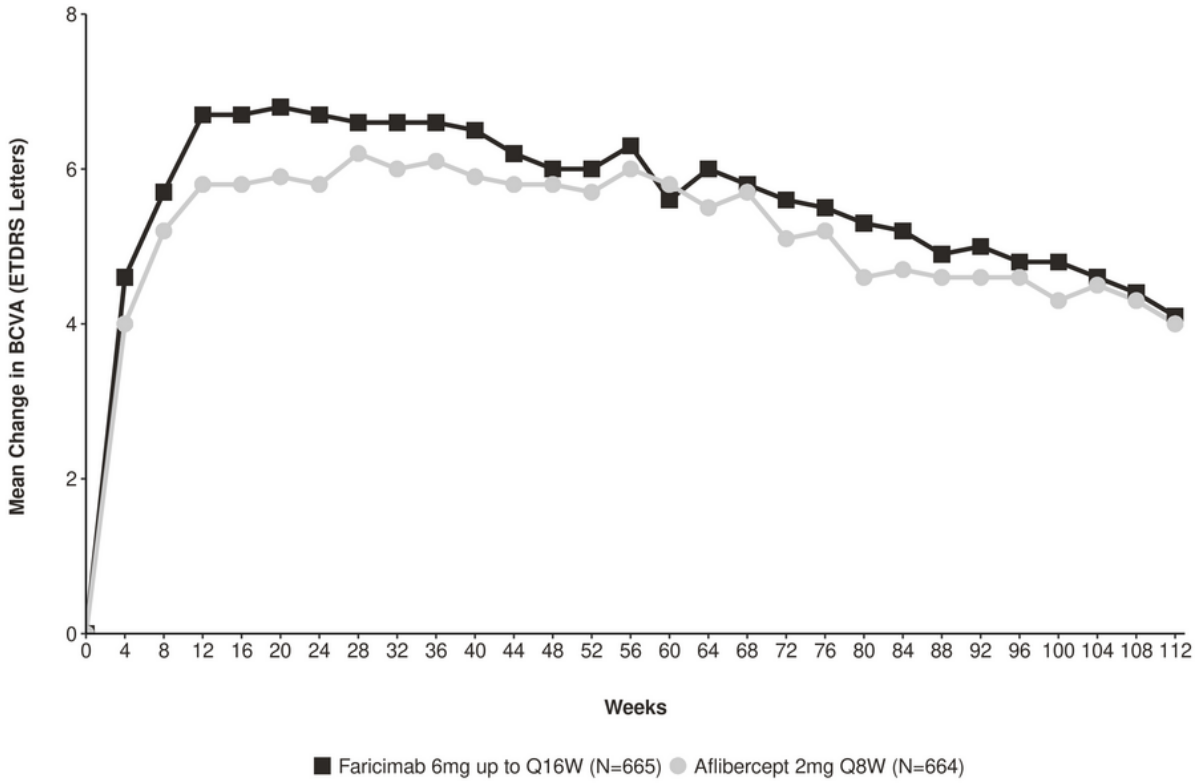
[a]Average of weeks 40, 44 and 48; [b]Average of weeks 104, 108, 112
BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
CI: Confidence Interval
LS: Least Square
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.

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

Efficacy Outcomes	**LUCERNE**			
	Year 1		**Year 2**	
	Faricimab up to Q16W N = 331	Aflibercept Q8W N = 327	Faricimab up to Q16W N = 331	Aflibercept Q8W N = 327
Mean change in BCVA as measured by ETDRS letter score from baseline (95% CI)	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)	0.0 (-1.7, 1.8)		-0.2 (-2.4, 2.1)	
Proportion of patients with ≥ 15 letter gain from baseline (CMH weighted proportion, 95% CI)	20.2% (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)	-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)	95.8% (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)	-1.5% (-4.4%, 1.3%)		-0.2% (-4.4%, 3.9%)	

[a]Average of weeks 40, 44 and 48; [b]Average of weeks 104, 108, 112
BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
CI: Confidence Interval
LS: Least Square
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.

Figure 1: Mean change in visual acuity from baseline to year 2 (week 112); combined data from TENAYA and LUCERNE studies



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

At week 60, 46% of patients in both TENAYA and LUCERNE were on a Q16W interval. Of these, 69% of patients in both studies maintained Q16W through week 112 without 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% of patients, respectively, maintained a ≥ Q12W interval through week 112 without an interval reduction below Q12W.

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

At week 60, 20% and 22% of patients in TENAYA and LUCERNE, respectively, were on a Q8W interval. Of these, 34% and 30% of patients 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.

Across studies, faricimab up to Q16W showed improvement in pre-specified efficacy endpoint of mean change from baseline to week 48 in the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) composite score that was comparable to aflibercept Q8W, and exceeded the threshold of 4 points. The magnitude of these changes corresponds to a 15-letter gain in BCVA.

The incidence of ocular adverse events in the study eye was 53.9% and 52.1% and non-ocular adverse events was 73.3% and 74.3%, through week 112 in the faricimab and aflibercept arms, respectively (see section 4.4 and 4.8).

DME

The safety and efficacy of faricimab were assessed in two randomised, multi-centre, double-masked, active comparator-controlled 2-year non-inferiority studies (YOSEMITE and RHINE) in patients with DME. A total of 1,891 patients were enrolled in the two studies with 1,622 (86%) patients completing the studies through week 100. A total of 1,887 patients were treated with at least one dose through week 56 (1,262 with faricimab). Patient ages ranged from 24 to 91 with a mean [SD] of 62.2 [9.9] 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 randomised in a 1:1:1 ratio to one of the three treatment regimens:

- Faricimab 6 mg Q8W after the first 6 monthly doses.
- Faricimab 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 followed a standardised treat-and-extend approach. The interval could be increased in 4-week increments or decreased in 4- or 8-week increments based on anatomic and/or visual outcomes, using data obtained only at study drug dosing visits.

Results

Both studies showed efficacy in the primary endpoint, defined as the mean 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, faricimab up to Q16W treated patients had a non-inferior 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.

After 4 initial monthly doses, the patients in the faricimab 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 faricimab 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 faricimab 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 4, Table 5, and Figure 2 below.

Table 4: Efficacy outcomes at the year 1 primary endpoint visits[a] and at year 2[b] in YOSEMITE

Efficacy Outcomes	YOSEMITE					
	Year 1			Year 2		
	Faricimab Q8W N = 315	Faricimab up to Q16W adjustable dosing N = 313	Aflibercept Q8W N = 312	Faricimab Q8W N = 262	Faricimab up to Q16W adjustable dosing N = 270	Aflibercept Q8W N = 259
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)
Difference in LS mean (97.5% CI year 1, 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)	
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%)
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%)	
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%)
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%)	

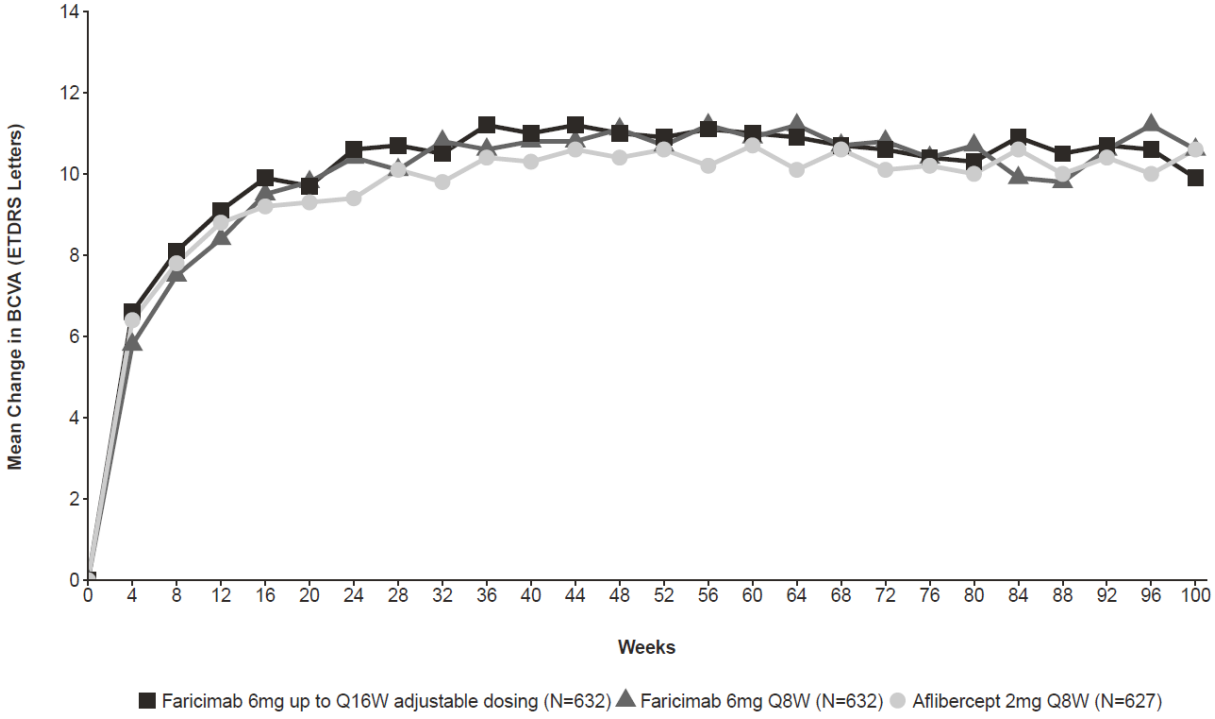
[a]Average of weeks 48, 52, 56; [b]Average of weeks 92, 96, 100
BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LS: Least Square
CI: Confidence Interval
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary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

Table 5: Efficacy outcomes at the year 1 primary endpoint visits[a] and at year 2[b] in RHINE

Efficacy Outcomes	RHINE					
	Year 1			Year 2		
	Faricimab Q8W N = 317	Faricimab up to Q16W adjustable dosing N = 319	Aflibercept Q8W N = 315	Faricimab Q8W N = 259	Faricimab 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)	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, 95% CI year 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)	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)	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)	98.9% (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)	0.3% (-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
LS: Least Square
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 faricimab Q8W vs. aflibercept comparison, however the corresponding CMH weighted % for faricimab adjustable vs. aflibercept comparison is similar to the one shown above.

Figure 2: Mean change in visual acuity from baseline to year 2 (week 100); combined data from YOSEMITE and RHINE studies



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, faricimab 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. Faricimab 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 faricimab Q8W, faricimab up to Q16W adjustable dosing, and aflibercept Q8W experienced a clinically meaningful improvement of $\geq$ 4-points from baseline to week 52 in the NEI VFQ-25 composite score, a pre-specified efficacy endpoint. These results were maintained at week 100.

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

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

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

The proportion of patients who achieved $\geq$ 2-step and $\geq$ 3-step improvement from baseline in ETDRS-DRSS at week 52 and at week 96 are shown in Table 6 and Table 7 below.

Table 6: 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 (DR evaluable population)

	YOSEMITE					
	52 Weeks			96 Weeks		
	Faricimab Q8W n = 237	Faricimab up to Q16W adjustable dosing n = 242	Aflibercept Q8W n = 229	Faricimab Q8W n = 220	Faricimab up to Q16W adjustable dosing n = 234	Aflibercept Q8W n = 221
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%
Weighted Difference (97.5% CI year 1, 95% year 2)	10.2% (0.3%, 20.0%)	6.1% (-3.6%, 15.8%)		9.1% (0.0%, 18.2%)	0.0% (-8.9%, 8.9%)	
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%
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%)	

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 faricimab Q8W vs. aflibercept comparison, however the corresponding CMH weighted % for faricimab adjustable vs. aflibercept comparison is similar to the one shown above.

Table 7: 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 RHINE (DR evaluable population)

	RHINE					
	52 Weeks			96 Weeks		
	Faricimab Q8W n = 231	Faricimab up to Q16W adjustable dosing n = 251	Aflibercept Q8W n = 238	Faricimab Q8W n = 214	Faricimab 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)	44.2%	43.7%	46.8%	53.5%	44.3%	43.8%
Weighted Difference (97.5% CI year 1, 95% year 2)	-2.6% (-12.6%, 7.4%)	-3.5% (-13.4%, 6.3%)		9.7% (0.4%, 19.1%)	0.3% (-8.9%, 9.5%)	
Proportion of patients with ≥ 3-step ETDRS-DRSS improvement from baseline (CMH weighted proportion)	16.7%	18.9%	19.4%	25.1%	19.3%	21.8%
Weighted Difference (95% CI year 1 and year 2)	-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 Faricimab Q8W vs. aflibercept comparison, however the corresponding CMH weighted % for Faricimab adjustable vs. aflibercept comparison is similar to the one shown above.

Treatment effects in evaluable subgroups (e.g. by previous anti-VEGF treatment, 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 consistently across all treatment arms in both studies.

The incidence of ocular adverse events in the study eye was 49.7%, 49.2% and 45.4% and non-ocular adverse events was 73.0%, 74.2%, and 75.7% through week 100, in the faricimab Q8W, faricimab up to Q16W, and aflibercept Q8W arms, respectively (see section 4.4 and 4.8).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with faricimab in all subsets of the paediatric population in nAMD and DME (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption and distribution

Based on a population pharmacokinetic analysis (including nAMD and DME N = 2,246), maximum free (unbound to VEGF-*A and Ang-2)* faricimab plasma concentrations (Cmax) are estimated to occur approximately 2 days post-dose. Mean (±SD [standard deviation]) plasma Cmax are estimated 0.23 (0.07) µg/mL and 0.22 (0.07) µg/mL respectively in nAMD and in DME patients. After repeated administrations, mean plasma free faricimab trough concentrations are predicted to be 0.002-0.003 µg/mL for Q8W dosing.

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

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

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

Biotransformation and elimination

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

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

Special populations

Elderly
In the four Phase III clinical studies, approximately 60% (1,149/1,929) of patients randomised to treatment with faricimab were ≥ 65 years of age. Population pharmacokinetic analysis has shown an effect of age on ocular pharmacokinetics of faricimab. The effect was considered not clinically meaningful. No dose adjustment is required in patients 65 years and above (see section 4.2).

Renal impairment
No specific studies in patients with renal impairment have been conducted with faricimab. 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 faricimab. No dose adjustment is required in patients with renal impairment (see section 4.2).

Hepatic impairment
No specific studies in patients with hepatic impairment have been conducted with faricimab. However, no special considerations are needed in this population because metabolism occurs via proteolysis and does not depend on hepatic function. No dose adjustment is required in patients with hepatic impairment (see section 4.2).

Other special populations

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

5.3 Preclinical safety data

No studies have been conducted on the carcinogenic or mutagenic potential of faricimab.

In pregnant cynomolgus monkeys, intravenous injections of faricimab resulting in serum exposure (Cmax) more than 500-times the maximum human exposure did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta, although, based on its pharmacological effect faricimab should be regarded as potentially teratogenic and embryo-/foetotoxic.

Systemic exposure after ocular administration of faricimab is very low.

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

6.2 Incompatibilities

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

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the vial in the outer carton in order 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.

6.5 Nature and contents of container

0.24 mL sterile, solution in a glass vial with a coated rubber stopper sealed with an aluminum 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, 5 µm).

6.6 Special precautions for disposal and other handling

Do not shake.

The vial contains more than the recommended dose of 6 mg. The fill volume of the vial (0.24 mL) is not to be used in total. The excess volume should be expelled prior to injection. Injecting the entire volume of the vial results in overdose. The injection dose must be set to the 0.05 mL dose mark, i.e. 6 mg faricimab.

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

The contents of the vial and the 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. Detailed instructions for use are provided in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1683/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 September 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu/en.