Please visit www.roche.com.sg/pharma/vabysmo for a printable version of this leaflet.

INJ-VAB-2025 12

# Vabysmo®

faricimab

## 1. DESCRIPTION

### 1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Pharmacotherapeutic group: Ophthalmologicals/Other ocular vascular disorder agents
ATC code: S01LA09

### 1.2 TYPE OF DOSAGE FORM

Solution for injection

### 1.3 ROUTE OF ADMINISTRATION

Intravitreal

### 1.4 STERILE / RADIOACTIVE STATEMENT

Sterile Product

### 1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

*Active ingredient(s):* faricimab

Excipients: L-histidine, acetic acid, L-methionine, sodium chloride, sucrose, polysorbate 20 and water for injection

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

Vabysmo for injection is a clear to opalescent, colorless to brownish-yellow solution, available in a single-dose glass vial or single-dose pre-filled syringe.

Each vial contains 28.8 mg faricimab in 0.24 mL solution. Each pre-filled syringe contains 21 mg faricimab in 0.175 mL solution. This provides a usable amount to deliver a single dose of 0.05 mL solution containing 6 mg of faricimab.

## 2. CLINICAL PARTICULARS

### 2.1 THERAPEUTIC INDICATION(S)

Vabysmo is indicated for the treatment of adult patients with:

- neovascular (wet) age-related macular degeneration (nAMD) (see section 3.1.2 Clinical Efficacy Studies).
- visual impairment due to diabetic macular edema (DME) (see section 3.1.2 Clinical Efficacy Studies).
- macular edema secondary to retinal vein occlusion (RVO) (see section 3.1.2 Clinical Efficacy Studies).

### 2.2 DOSAGE AND ADMINISTRATION

**General**

For intravitreal injection only. Vabysmo must be administered by a qualified physician experienced in intravitreal injections. Each vial or pre-filled syringe 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 solution) administered by intravitreal injection every 4 weeks for the first 3 doses. Thereafter, an assessment of disease activity based on anatomic and visual acuity evaluations is recommended 16 and/or 20 weeks after treatment initiation so that the dosing interval may be modified using a treat-and-extend approach. In patients without disease activity, administration of faricimab every 16 weeks should be considered. In patients with disease activity, treatment every 8 weeks or 12 weeks should be considered. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly by increase of up to 4-week intervals or decrease of up to 8-week intervals. Interval reduction should be implemented if anatomic and/or visual outcomes deteriorate. (see section 3.1.2 Clinical Efficacy Studies).

Patients should be assessed regularly. 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 solution) administered by intravitreal injection every 4 weeks for at least 3 doses; more consecutive monthly injections may be needed until macular edema is resolved based on the central subfield thickness (CST) of the macula as measured by optical coherence tomography. Thereafter, the dosing interval may be modified using a treat-and-extend approach based on anatomic and/or visual acuity outcomes at dosing visits. The dosing interval may be extended in increments of up to 4 weeks to every 16 weeks. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and dosing interval reductions of up to 8 weeks may be implemented if deemed necessary (see section 3.1.2 Clinical Efficacy Studies).

Patients should be assessed regularly. Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion.

**Macular edema secondary to retinal vein occlusion (RVO)**

The recommended dose for Vabysmo is 6mg (0.05 mL solution) administered by intravitreal injection every 4 weeks; 3 or more consecutive monthly injections may be needed. Thereafter, the dosing interval may be modified using a treat-and-extend approach based on anatomic and/or visual acuity outcomes at dosing visits. The dosing interval may be extended in up to 4-week increments. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reduction should be implemented if anatomic and/or visual outcomes deteriorate (see section 3.1.2 Clinical Efficacy Studies). Treatment intervals longer than 16 weeks between injections have not been studied.

Patients should be assessed regularly. 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, and if present, the vial should not be used.

The injection procedure must be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Adequate anesthesia 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.

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. 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.

**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.

#### 2.2.1 Special Dosage Instructions

**Pediatric use**

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

**Geriatric use**

No dose adjustment is required in patients ≥ 65 years of age (see section3.2.5 Pharmacokinetics in Special Populations).

**Renal Impairment**

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.

### 2.3 CONTRAINDICATIONS

Vabysmo is contraindicated in patients with ocular or periocular infections.

Vabysmo is contraindicated in patients with active intraocular inflammation.

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

### 2.4 WARNINGS AND PRECAUTIONS

#### 2.4.1 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, retinal tear and iatrogenic traumatic cataract. 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.

**Intraocular pressure increases**

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including those with Vabysmo. Sustained (present at 2 or more consecutive visits) IOP increases >21 mm Hg have also been reported. Vabysmo has not been studied in patients with poorly controlled glaucoma. 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, including Vabysmo, and there is a theoretical risk that these may be related to VEGF inhibition. A low incidence rate of arterial thromboembolic events was observed in the faricimab clinical trials in patients with nAMD, DME, and RVO.

There is limited data on the safety of Vabysmo in patients with history of stroke or transient ischemic attack or myocardial infarction.

**Immunogenicity**

As this is a therapeutic protein, there is the potential for immunogenicity with Vabysmo (see section 2.6 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 or other therapies (e.g., photodynamic therapy) for the treatment of nAMD or DME in the same eye. Vabysmo 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.
- 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 tear has been reported with the use of Vabysmo (see section 2.6 Undesirable Effects). 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**

In nAMD clinical studies, there is limited data on patients with a total lesion size >9 disc areas on fundus fluorescein angiography. 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, DME, and RVO patients with active systemic infections. There is also no experience of treatment with Vabysmo in diabetic and RVO patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

#### 2.4.2 Ability to drive and use machines

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

### 2.5 USE IN SPECIAL POPULATIONS

#### 2.5.1 Females and Males of Reproductive Potential

*Fertility*

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

*Contraception*

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

#### 2.5.2 Pregnancy

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

No adverse effects were observed in a study in pregnant cynomolgus 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 3.3.4 Reproductive Toxicity).

It is not known whether Vabysmo can cross the placenta or cause harm to the fetus when administered to pregnant women. The systemic exposure to Vabysmo is low after ocular administration, but due to the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. 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.

#### 2.5.3 Lactation

It is not known whether Vabysmo is excreted in human breast milk. No studies have been conducted to assess the impact of Vabysmo on milk production or its presence in breast milk. Because many drugs are excreted in human milk with the potential for absorption and harm to infant growth and development exists, as precautionary measure, breastfeeding is not recommended during the use of Vabysmo.

### 2.6 UNDESIRABLE EFFECTS

#### 2.6.1 Clinical Trials

**Summary of the safety profile**

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

**Treatment of nAMD**

The most frequently reported serious adverse reactions in patients treated with Vabysmo were retinal pigment epithelial (RPE) tear (0.6%), cataract (0.5%), endophthalmitis (0.5%), uveitis (0.5%), and visual acuity reduced (0.3%).

The most frequently reported adverse reactions in patients treated with Vabysmo were conjunctival haemorrhage (8.9%), cataract (8.7%), vitreous detachment (5.1%), vitreous floaters (4.5%), IOP increased (4.1%), eye pain (3.8%) and RPE tear (2.9%).

The adverse reactions (regardless of causality) leading to permanent discontinuation of Vabysmo were endophthalmitis, uveitis, iridocyclitis, vitritis, and RPE tear.

**Treatment of DME**

The most frequently reported serious adverse reactions in patient treated with Vabysmo were cataract (1%), endophthalmitis (0.5%), uveitis (0.2%), retinal tear (0.2%) and vitreous haemorrhage (0.2%).

The most frequently reported adverse reactions in patients treated with Vabysmo were cataract (15%), conjunctival haemorrhage (8%), vitreous detachment (5%), vitreous floaters (4%), IOP increased (4%) and eye pain (3%).

The most frequently reported adverse reactions (regardless of causality) leading to permanent discontinuation of Vabysmo was uveitis.

**Treatment of RVO**
The most frequently reported serious adverse reaction in patients treated with Vabysmo was uveitis (0.5%), vitreous haemorrhage (0.3%), rhegmatogenous retinal detachment (0.3%), iridocyclitis (0.2%), visual acuity reduced (0.2%), vitritis (0.2%) and retinal tear (0.2%).

The most frequently reported adverse reactions in patients treated with Vabysmo were conjunctival hemorrhage (6%), IOP increased (5%), cataract (4%), vitreous detachment (4%), eye pain (3%), vitreous floaters (2%), visual acuity reduced (1%) and vitritis (1%).

The adverse reactions (regardless of causality) leading to permanent discontinuation of Vabysmo was uveitis, vitritis and rhegmatogenous retinal detachment.

**Tabulated summary of adverse drug reactions from clinical trials**
Due to the widely varying conditions between studies, the adverse reaction profiles and frequencies reported from the development studies of Vabysmo cannot be directly compared to those reported in other development programs.

**Neovascular (wet) aged-related macular degeneration (nAMD)**
The data described below reflect exposure to Vabysmo in 664 patients with nAMD treated with the 6 mg dose in the two randomized, double-masked, active comparator (aflibercept 2mg every 8 weeks) controlled clinical studies (TENAYA and LUCERNE) through week 112 (see section 3.1.2 Clinical Efficacy Studies).

**Table 1 Adverse Reactions (≥ 1%) in the TENAYA and LUCERNE nAMD Studies through Week 112**

| Adverse Reactions SOC Preferred Term MedDRA version 23.1 | Baseline to Week 60 | | Baseline to Week 112 | |
|---|---|---|---|---|
| | Vabysmo n = 664 | Aflibercept n = 662 | Vabysmo n = 664 | Aflibercept n = 662 |
| **Eye disorders** | | | | |
| Conjunctival haemorrhage | 8% | 8% | 9% | 9% |
| Cataract | 5% | 3% | 9% | 8% |
| Vitreous detachment | 4% | 3% | 5% | 5% |
| Vitreous floaters | 3% | 2% | 5% | 3% |
| Retinal pigment epithelial tear | 3% | 2% | 3% | 2% |
| Intraocular pressure increased | 3% | 3% | 4% | 4% |
| Eye pain | 3% | 3% | 4% | 4% |
| Intraocular inflammation[a] | 2% | < 1% | 3% | 1% |
| Eye irritation | 1% | < 1% | 2% | 1% |
| Corneal abrasion | 1% | 1% | 2% | 2% |
| Ocular discomfort | 1% | < 1% | 1% | < 1% |
| Eye pruritus | < 1% | < 1% | 1% | < 1% |
| Ocular hyperaemia | < 1% | < 1% | 1% | < 1% |
| Vision blurred | < 1% | < 1% | 1% | < 1% |

[a]Including iridocyclitis, iritis, uveitis and vitritis

**Diabetic Macular Edema (DME)**
The data described below reflect exposure to Vabysmo in 1,262 patients with DME treated with the 6 mg dose in the two randomized, double-masked, active comparator (aflibercept 2 mg every 8 weeks) controlled clinical studies (YOSEMITE and RHINE) through Week 100 (see section 3.1.2 Clinical Efficacy Studies).

**Table 2 Adverse Reactions (≥ 1%) in the YOSEMITE and RHINE DME Studies through Week 100**

| Adverse Reaction SOC Preferred Term MedDRA version 23.1 | Baseline to Week 56 | | Baseline to Week 100 | |
|---|---|---|---|---|
| | Vabysmo n = 1,262 | Aflibercept n = 625 | Vabysmo n = 1,262 | Aflibercept n = 625 |
| **Eye disorders** | | | | |
| Cataract | 5% | 5% | 15% | 12% |
| Conjunctival haemorrhage | 7% | 6% | 8% | 7% |
| Vitreous detachment | 3% | 3% | 5% | 4% |
| Vitreous floaters | 3% | 2% | 4% | 3% |
| Intraocular pressure increased | 3% | 2% | 4% | 3% |
| Eye pain | 2% | 3% | 3% | 3% |
| Intraocular inflammation[a] | 1% | < 1% | 1% | < 1% |
| Lacrimation increased | < 1% | < 1% | 1% | < 1% |
| Vitreous haemorrhage | 1% | < 1%- | < 1% | < 1% |

[a]Including iridocyclitis, iritis, uveitis and vitritis

**Retinal Vein Occlusion (RVO)**
The data described below reflect exposure to Vabysmo in 641 patients with RVO treated with the 6 mg dose in the two randomized, double-masked, active comparator (aflibercept 2 mg every 4 weeks) controlled clinical studies (BALATON and COMINO) from baseline to Week 24 (controlled) and from baseline to Week 72 (no control arm from Week 24) (see section 3.1.2 Clinical Efficacy Studies).

**Table 3 Adverse Reactions (≥ 1%) in the BALATON and COMINO RVO Studies through Week 24 and Week 72**

| Adverse Reaction SOC Preferred Term MedDRA version 25.0 | Baseline to Week 24 | | Baseline to Week 72[b] |
|---|---|---|---|
| | Vabysmo n = 641 | Aflibercept n = 635 | Vabysmo n=641 |
| **Eye disorders** | | | |
| Cataract | <1% | 1% | 4% |
| Conjunctival haemorrhage | 3% | 4% | 6% |
| Eye pain | <1% | <1% | 3% |
| Visual acuity reduced | <1% | <1% | 1% |
| Vitreous detachment | 2% | 2% | 4% |
| Vitreous floaters | 2% | 2% | 2% |
| Intraocular pressure increased | 1% | 3% | 5% |
| Intraocular inflammation[a] | 1% | <1% | 3% |

[a]Including iridocyclitis, iritis, uveitis and vitritis
[b]Represents patients treated with Vabysmo from baseline to 72 Weeks

**Description of selected adverse drug reactions from clinical trials**
**Arterial Thromboembolic Events (ATEs)**
The incidence of reported ATEs in the nAMD studies during Week 112 was 3% (22 out of 664) in patients treated with Vabysmo compared with 3% (20 out of 662) in patients treated with aflibercept (see 3.1.2 Clinical Efficacy Studies).

The incidence of reported ATEs in the DME studies from baseline to Week 100 was 5% (64 out of 1,262) in patients treated with Vabysmo compared with 5% (32 out of 625) in patients treated with aflibercept (see 3.1.2 Clinical Efficacy Studies).

The incidence of reported ATEs in the RVO studies from baseline to Week 24 was 1% (7 out of 641) in patients treated with Vabysmo compared with 1% (9 out of 635) in patients treated with aflibercept (see 3.1.2 Clinical Efficacy Studies). The incidence of reported ATEs from baseline to Week 72 was 2.8% (18 out of 641) in patients treated with Vabysmo.

**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.

There is potential for an immune response in patients treated with Vabysmo (see section 2.4 Warning and Precautions). After dosing with Vabysmo, treatment-emergent anti-faricimab antibodies (ADA) were detected in approximately 13.8% of nAMD patients,9.6% of DME and 14.4% of RVO patients randomized to faricimab. The clinical significance of anti-faricimab antibodies on safety is unclear at this time. The incidence of intraocular inflammation adverse reactions were observed in 12 out of 98 (nAMD),15 out of 128 (DME) and 9 out of 95 (RVO) ADA-positive patients and in 8 out of 562 (nAMD),5 out of 1124 (DME) and 10 out of 543 (RVO) ADA-negative patients however, the overall incidence of anti-faricimab antibody positivity and intraocular inflammation in the entire trial population is approximately 1%. The incidence of serious ocular adverse reactions in anti-faricimab antibody positive patients was 6 out of 98 (nAMD),14 out of 128 (DME), and 7 out of 95 (RVO), and in anti-faricimab antibody negative patients was 23 out of 562 (nAMD), 45 out of 1124 (DME), and 34 out of 543 (RVO). Anti-faricimab antibodies were not associated with an impact on clinical efficacy or systemic pharmacokinetics.

**Retinal pigment epithelial (RPE) tear**
Retinal pigment epithelial (RPE) tear is a complication of pigment epithelial detachment (PED) in patients with nAMD. 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 were mild to moderate, without impact to vision and occurred during the loading phase. Serious RPE tear was reported in 4 patients (0.6%) in faricimab group and none in aflibercept group. Three of the serious RPE Tear events in faricimab group were associated with vision loss of ≥ 15 ETDRS letters.

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

Eye disorders: retinal vasculitis, retinal occlusive vasculitis

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

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

## 2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No drug-drug interaction studies have been performed with Vabysmo.

# 3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
## 3.1 PHARMACODYNAMIC PROPERTIES
### 3.1.1 Mechanism of Action
Faricimab is a humanized bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of both Ang-2 and vascular endothelial growth factor A (VEGF-A). By inhibiting VEGF-A, faricimab suppresses endothelial cell proliferation, neovascularization and vascular permeability. By inhibiting Ang-2, faricimab is thought to promote vascular stability and desensitize blood vessels to the effects of VEGF-A. Ang-2 levels are increased in some patients with nAMD and DME.

**Pharmacodynamics**

Following intravitreal administration of faricimab in nAMD,DME, and RVO patients, free Ang-2 and VEGF-A in aqueous humor was reduced. No apparent suppression of VEGF-A and Ang-2 was observed in plasma.

Reductions in mean central subfield thickness (CST) from baseline were observed in patients with nAMD or DME treated with Vabysmo in the six clinical trials (TENAYA, LUCERNE, RHINE, YOSEMITE, BALATON, and COMINO).

In nAMD patients, the mean CST change from baseline to the primary endpoint visits (averaged at Weeks 40, 44, and 48) for Vabysmo versus aflibercept (Q8W) was -137 µm vs. -129 µm (TENAYA) and -137µm vs. -131µm (LUCERNE). These mean CST reductions were maintained through year 2.

In DME patients treated with Vabysmo Q8W or Vabysmo up to Q16W adjustable dosing versus aflibercept Q8W, the mean change in CST from baseline was -207 µm and -197 µm vs. -170 µm (YOSEMITE) and -196 µm, -188 µm vs. -170 µm (RHINE) at the primary endpoint visits (averaged at Weeks 48, 52 and 56); and -216 µm, -205 µm vs. -196 µm (YOSEMITE) and -203 µm, -197 µm vs. -186 µm (RHINE) averaged at Weeks 92, 96 and 100.

In RVO patients, the mean change in CST from baseline to week 24 for Vabysmo (Q4W) versus aflibercept (Q4W) was -311 µm vs. -304 µm (BALATON) and -462 µm vs -449 µm (COMINO). CST reductions were maintained through week 72 when patients moved to a Vabysmo up to Q16W adjustable dosing regimen.

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

In both studies, patients were randomized in a 1:1 ratio to one of two treatment arms:
- Vabysmo 6 mg up to Q16W after four initial monthly doses
- Aflibercept 2 mg Q8W after three initial monthly doses

After the first four monthly doses (weeks 0, 4, 8, and 12) patients randomized to the Vabysmo arm received Q16W, every 12 weeks (Q12W) or Q8W dosing based on an assessment of disease activity at weeks 20 and 24, using objective pre-specified ETDRS-measured BCVA and SD-OCT CST 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 intervals (up to Q16W) or could be decreased 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.

The primary efficacy endpoint was the mean change in BCVA from baseline based on an average at Weeks 40, 44, and 48, measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score. The secondary endpoints included proportion of patients gaining ≥ 15 letters in BCVA from baseline based on an average at Weeks 40, 44 and 48. In both studies (TENAYA and LUCERNE), non-inferiority of Vabysmo compared to aflibercept Q8W was demonstrated using mean change in BCVA from baseline at year 1, and these vision gains were maintained through week 112. Detailed results of both studies are shown in Table 4, 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% and 45%
- Q12W: 34% and 33%
- Q8W: 20% and 22%

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 4 Baseline Characteristics[a] and Efficacy outcomes at the primary endpoint visits[b] and at year 2[c] 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 |
| Median number of injections received [Q1, Q3] | 6.0 [6, 7] | 8.0 [7, 8] | 3.0 [3, 5] | 6.0 [6, 6] | 6.0 [6, 7] | 8.0 [7, 8] | 3.0 [3, 5] | 6.0 [6, 6] |
| Mean BCVA [SD] ETDRS letters at baseline | 61.3 [12.5] | 61.5 [12.9] | | | 58.7 [14.0] | 58.9 [13.3] | | |
| Mean CST [SD] (microns) at baseline | 360.5 [124.1] | 356.1 [107.0] | | | 353.1 [120.1] | 359.0 [131.1] | | |
| Mean CNV lesion size [SD] ($mm^2$) at baseline | 4.7 [4.8] | 4.5 [4.1] | | | 4.7 [4.7] | 4.3 [4.3] | | |
| 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][d] | | 0.4 [-1.9, 2.8] | | 0.0 [-1.7, 1.8][d] | | -0.2 [-2.4, 2.1] | |
| Proportion of patients with ≥ 15 letter gain from baseline | 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%] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| [CMH weighted proportion, 95% CI] | | | | | | | | |
| 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]Baseline ocular characteristics were well balanced between treatment arms and across studies
[b]Average of weeks 40, 44 and 48; [c]Average of weeks 104, 108, 112
[d]Met the pre-specified non-inferiority margin of 4 letters for the primary endpoint in both studies
Median number of injections received for Year 1 corresponds to the period of baseline through week 48, and for Year 2 corresponds to the period after Week 60 until End of Study.
Q1: 1st quartile
Q3: 3rd quartile
BCVA: Best Corrected Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; CST: Central Subfield Thickness measured from internal limiting membrane to retinal pigment epithelium membrane; CNV: Choroidal Neovascularisation
SD: Standard Deviation
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**

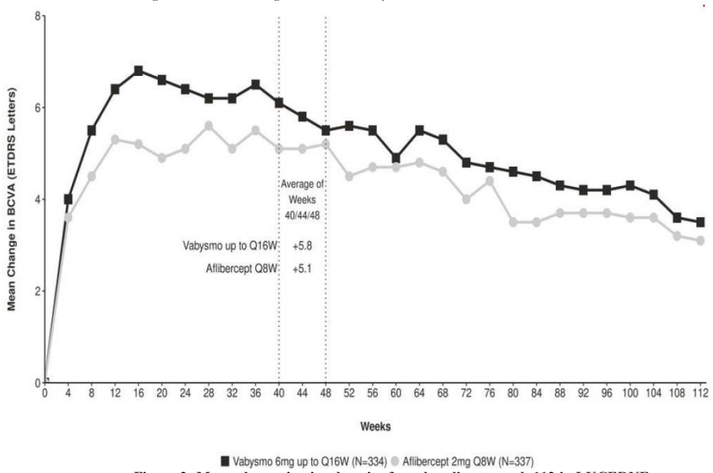
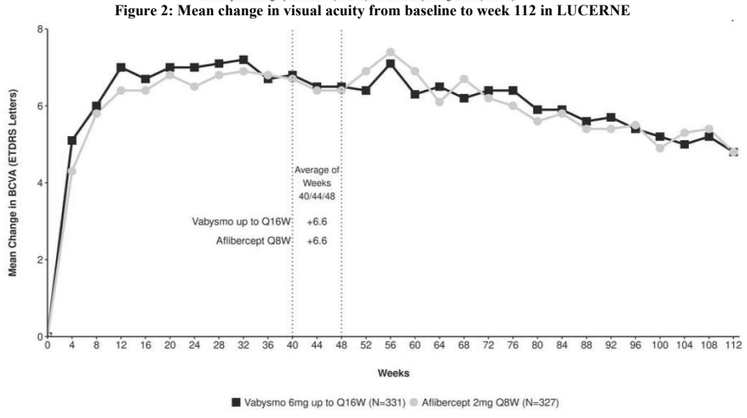



**Figure 2: Mean change in visual acuity from baseline to week 112 in LUCERNE**




**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 (85.8%) patients completing the studies through week 100. A total of 1,887 patients were treated with at least one dose through week 56 (1,262 with Vabysmo). Patient ages ranged from 24 to 91 with a mean of 62.2 years. The overall population included both anti-VEGF naive patients (78%) and patients who had been previously treated with a VEGF inhibitor prior to study participation (22%). In both studies, patients were randomized in a 1:1:1 ratio to one of the three treatment regimens:

- Vabysmo 6 mg Q8W after the first 6 monthly doses.
- Vabysmo 6 mg up to Q16W adjustable dosing administered in 4, 8, 12 or 16 week intervals after the first 4 monthly doses.
- Aflibercept 2 mg Q8W after the first 5 monthly doses.

In the Q16W adjustable dosing arm, the dosing followed a standardized treat-and-extend approach. The interval could be increased in 4-week increments or decreased in 4- or 8-week increments based on CST change as measured on OCT and/or BCVA change as measured by ETDRS letters, using data obtained only at study drug dosing visits.

The primary efficacy endpoint was the mean change in BCVA from baseline based on an average at Weeks 48, 52 and 56, measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. The additional visual acuity secondary endpoint was the proportion of patients gaining ≥ 15 letters in BCVA from baseline based on an average at Weeks 48, 52 and 56.

In both studies, (YOSEMITE and RHINE), non-inferiority of Vabysmo Q8W compared to aflibercept Q8W and of Vabysmo variable dosing compared to aflibercept Q8W was demonstrated using mean change in BCVA from baseline at Year 1, respectively. The results are summarized in Table 5, 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, respectively. The proportion of patients in YOSEMITE and RHINE, respectively, who received >15 injections in the PTI arms through Week 96 was 13% and 18%.

Detailed results from the analyses of YOSEMITE and RHINE studies are listed in Table 5 and Figures 3 and 4 below.

**Table 5 Baseline Characteristics[a] and Efficacy outcomes at the year 1 primary endpoint visits[b] and at year 2[c] in YOSEMITE and RHINE**

| Efficacy Outcomes | YOSEMITE | | | | | | RHINE | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Year 1 | | | Year 2 | | | Year 1 | | | Year 2 | | |
| | Vabysmo Q8W N = 315 | Vabysmo up to Q16W adjustable dosing N = 313 | Aflibercept Q8W N = 312 | Vabysmo Q8W N = 315 | Vabysmo up to Q16W adjustable dosing N = 313 | Aflibercept Q8W N = 312 | Vabysmo Q8W N = 317 | Vabysmo up to Q16W adjustable dosing N = 319 | Aflibercept Q8W N = 315 | Vabysmo Q8W N = 317 | Vabysmo up to Q16W adjustable dosing N = 319 | Aflibercept Q8W N = 315 |
| Mean BCVA [SD] at baseline | 62.0 [9.9] | 61.9 [10.2] | 62.2 [9.5] | | | | 61.9 [10.1] | 62.5 [9.3] | 62.1 [9.4] | | | |
| Mean CST [SD] (microns) at baseline | 492.3 [135.8] | 485.8 [130.8] | 484.5 [131.1] | | | | 466.2 [119.4] | 471.3 [127.0] | 477.3 [129.4] | | | |
| Mean time since DME diagnosis [SD] (months) at baseline. | 14.0 [21.7] | 17.6 [36.2] | 17.5 [27.6] | | | | 18.9 [32.2] | 20.7 [33.0] | 20.3 [37.1] | | | |
| Mean HbA1c [SD] (%) at baseline | 7.6 [1.1] | 7.6 [1.1] | 7.6 [1.1] | | | | 7.6 [1.2] | 7.7 [1.2] | 7.7 [1.2] | | | |
| Type of Diabetes Mellitus % Type 1 Type 2 | 7.6 92.4 | 5.1 95.5 | 4.2 95.8 | | | | 6.3 93.7 | 6.0 94.0 | 5.4 94.6 | | | |
| Diabetic Retinopathy Status (%) DRS levels 10-20 (DR | 1.9 | 2.9 | 4.5 | | | | 1.5 | 4.4 | 2.2 | | | |
| Absent/ Questionable/ Microaneurysms only) DRS levels 35-43 (mild and moderate NPDR) DRS levels 47-53 (moderately severe and severe NPDR) DRS level 61-85 (PDR) Cannot grade Missing | 53.4 35.9 7.0 1.3 0.6 | 56.9 31.6 6.7 1.6 0.3 | 53.8 33.0 5.7 2.2 0.6 | | | | 56.2 34.4 6.3 0.6 0.9 | 51.4 31.0 11.6 1.6 0.0 | 54.9 33.3 6.4 1.6 1.6 | | | |
| Mean change in BCVA as measured by ETDRS letter score from baseline [97.5% CI year 1 and 95% 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, 95% CI year 2] | -0.2 [-2.0, 1.6][d] | 0.7 [-1.1, 2.5][d] | | -0.7 [-2.6, 1.2][d] | -0.7 [-2.5, 1.2][d] | | 1.5 [-0.1, 3.2][d] | 0.5 [-1.1, 2.1][d] | | 1.5 [-0.5, 3.6][d] | 0.7 [-1.3, 2.7][d] | |
| 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]Baseline ocular characteristics were well balanced between treatment arms and across studies
[b]Average of weeks 48, 52, 56; [c]Average of weeks 92, 96, 100
[d]Met the pre-specified non-inferiority margin of 4 letters for the primary endpoint at Year 1 in both studies
BCVA: Best Corrected Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; CST: Central Subfield Thickness measured from internal limiting membrane to Bruch's membrane; PDR: Proliferative Diabetic Retinopathy; NPDR: Non-Proliferative Diabetic Retinopathy; HbA1c: Haemoglobin A1c
CI: Confidence Interval
LS: Least Square
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.
Note: CMH weighted % for aflibercept arm presented for Vabysmo Q8W vs. aflibercept comparison, however the corresponding CMH weighted % for Vabysmo adjustable vs. aflibercept comparison is similar to the one shown above.

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

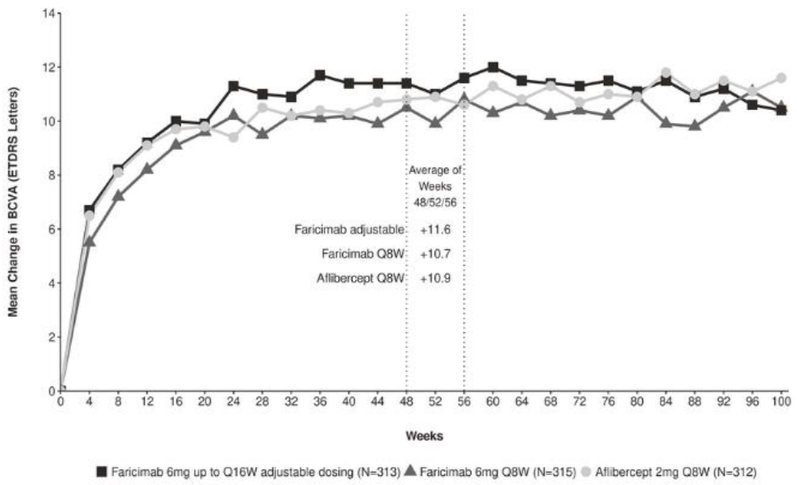
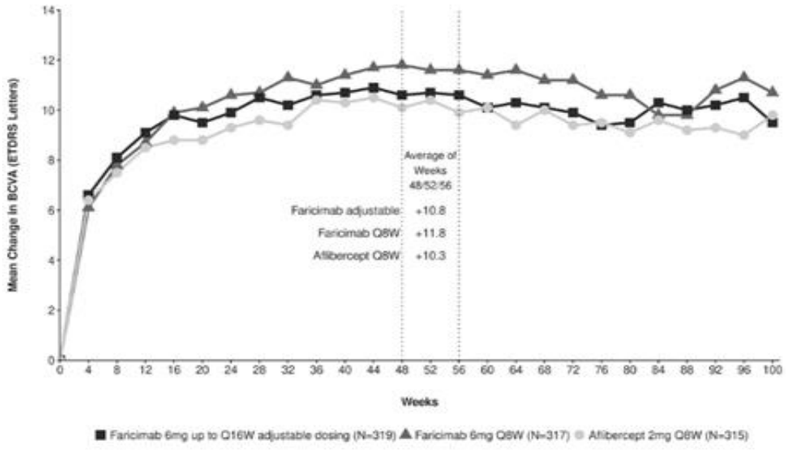



**Figure 4: Mean change in visual acuity from baseline to year 2 (week 100) in RHINE**




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 6 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 and RHINE (DR evaluable population)**

| | YOSEMITE | | | | | | RHINE | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 52 Weeks | | | 96 Weeks | | | 52 Weeks | | | 96 Weeks | | |
| | Vabysmo Q8W n = 237 | Vabysmo up to Q16W adjustable dosing n = 242 | Aflibercept Q8W n = 229 | Vabysmo Q8W n = 220 | Vabysmo up to Q16W adjustable dosing n = 234 | Aflibercept Q8W n = 221 | Vabysmo Q8W n = 231 | Vabysmo up to Q16W adjustable dosing n = 251 | Aflibercept Q8W n = 238 | Vabysmo Q8W n = 214 | Vabysmo up to Q16W adjustable dosing n = 228 | Aflibercept Q8W n = 203 |
| Proportion of patients with ≥2-step ETDRS-DRSS improvement from baseline (CMH weighted proportion) | 46.0% | 42.5% | 35.8% | 51.4% | 42.8% | 42.2% | 44.2% | 43.7% | 46.8% | 53.5% | 44.3% | 43.8% |
| Weighted Difference (97.5% CI year 1, 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%) | | -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) | 16.8% | 15.5% | 14.7% | 22.4% | 14.6% | 20.9% | 16.7% | 18.9% | 19.4% | 25.1% | 19.3% | 21.8% |
| Weighted Difference (95% CI year 1 and year 2) | 2.1% (-4.3%, 8.6%) | 0.6% (-5.8%, 6.9%) | | 1.5% (-6.0%, 9.0% | -6.7% -13.6%, 0.1% | | -0.2% (-5.8%, 5.3%) | -1.1% (-8.0%, 5.9%) | | 3.3% (-4.6%, 11.3%) | -2.7% (-10.2%, 4.8%) | |

ETDRS-DRSS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment of categorical variables.
CI: Confidence Interval
Note: CMH weighted % for aflibercept arm presented for VabysmoQ8W vs. aflibercept comparison, however the corresponding CMH weighted % for Vabysmo adjustable vs. aflibercept comparison is similar to the one shown above.

**Treatment of RVO**

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

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

In both studies, patients were randomized in a 1:1 ratio to one of two treatment arms:
- VABYSMO 6 mg Q4W for six consecutive monthly doses
- Aflibercept 2 mg Q4W for six consecutive monthly doses

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

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

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

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

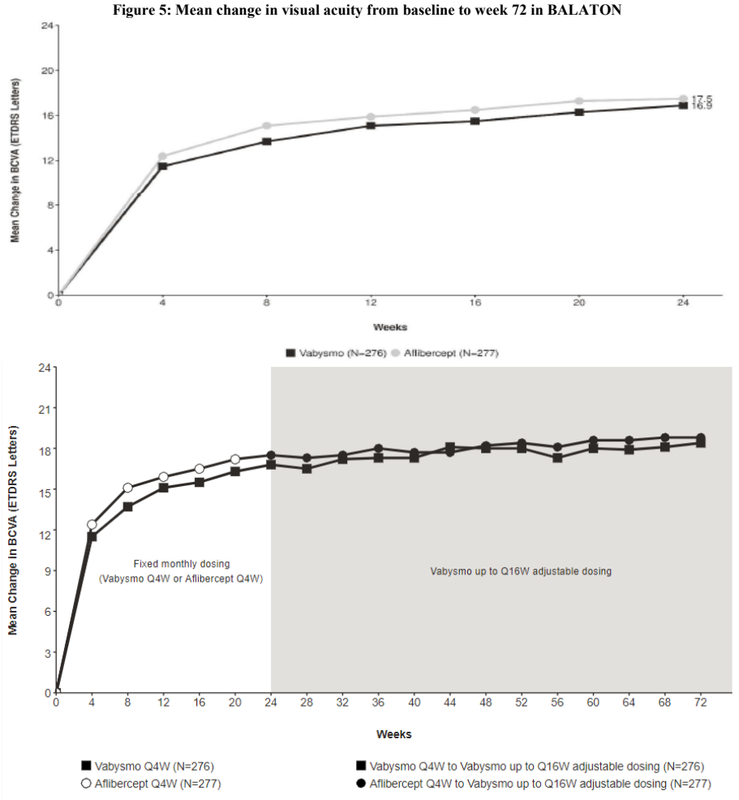
Detailed results of both studies are shown in Table 7, Figure 5 and Figure 6 below.

**Table 7: Baseline characteristics and efficacy outcomes at the week 24 primary endpoint visits and at the end of the study in BALATON and COMINO**

| Efficacy Outcomes | BALATON | | | | COMINO | | | |
|---|---|---|---|---|---|---|---|---|
| | 24 Weeks | | 72 Weeks[a] | | 24 Weeks | | 72 Weeks[a] | |
| | Vabysmo N = 276 | Aflibercept N = 277 | Vabysmo Q4W to Vabysmo Adjustable N = 276 | Aflibercept Q4W to Vabysmo Adjustable N = 277 | Vabysmo N = 366 | Aflibercept N = 363 | Vabysmo Q4W to Vabysmo Adjustable N = 366 | Aflibercept Q4W to Vabysmo Adjustable N = 363 |
| Median number of injections received [Q1, Q3] | 6.0 [6, 6] | 6.0 [6, 6] | 4.0 [3, 5] | 4.0 [3, 5] | 6.0 [6, 6] | 6.0 [6, 6] | 5.0 [3, 8] | 4.0 [3, 7] |
| Mean BCVA [SD] ETDRS letters at baseline | 57.5 [13.0] | 57.6 [12.2] | | | 50.3 [16.3] | 50.7 [16.3] | | |
| Mean CST [SD] (microns) at baseline | 558.3 [177.0] | 558.1 [180.3] | | | 702.2 [244.0] | 721.1 [242.9] | | |
| Mean change in BCVA as measured by ETDRS letter score from baseline [95% CI] | 16.9 [15.7, 18.1] | 17.5 [16.3, 18.6] | 18.1 [16.9, 19.4] | 18.8 [17.5, 20.0] | 16.9 [15.4, 18.3] | 17.3 [15.9, 18.8] | 16.9 [15.2, 18.6] | 17.1 [15.4, 18.8] |
| Difference in LS mean [95% CI] | -0.6 [-2.2, 1.1] | | | | -0.4 [-2.5, 1.6] | | | |
| Proportion of patients with ≥ 15 letter gain from baseline [CMH weighted proportion, 95% CI] | 56.1% [50.4%, 61.9%] | 60.4% [54.7%, 66.0%] | 61.5% [56.0%, 67.0%] | 65.8% [60.3%, 71.2%] | 56.6% [51.7%, 61.5%] | 58.1% [53.3%, 62.9%] | 57.6% [52.8%, 62.5%] | 59.5 [54.7%, 64.3%] |
| Difference in CMH weighted % [95% CI] | -4.3% [-12.3%, 3.8%] | | | | -1.5% [-8.4%, 5.3%] | | | |

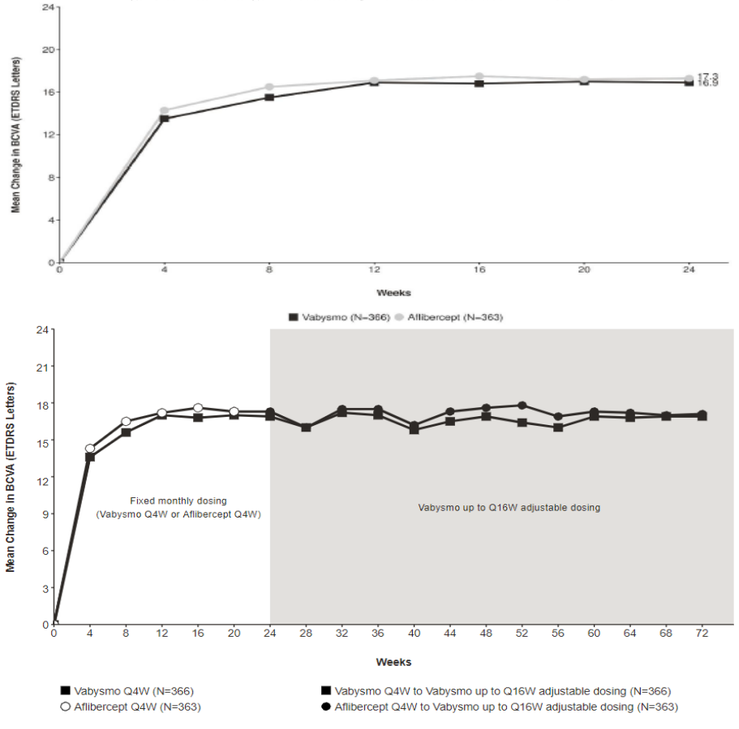
[a]Average of weeks 64, 68, 72
BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
CI: Confidence Interval
LS: Least Square
CMH: Cochran–Mantel–Haenszel method; a statistical test that generates an estimate of an association with a binary outcome and is used for assessment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

**Figure 5: Mean change in visual acuity from baseline to week 72 in BALATON**




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

**Figure 6: Mean change in visual acuity from baseline to week 72 in COMINO**




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

## 3.2 PHARMACOKINETIC PROPERTIES

### 3.2.1 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 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.

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

### 3.2.2 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 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.

No apparent suppression of Ang-2 or VEGF-A was observed in plasma.

### 3.2.3 Metabolism

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

### 3.2.4 Elimination

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

### 3.2.5 Pharmacokinetics in Special Populations

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

*Geriatric Population*
In the six Phase III clinical studies, approximately 58% (1,496/2,571) of patients 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 with Vabysmo in patients with renal impairment. Pharmacokinetic analysis of patients in all clinical studies of which 63% had renal impairment (mild 38%, moderate 23%, and severe 2%), revealed no differences with respect to systemic pharmacokinetics of faricimab after intravitreal administration of Vabysmo.

*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.

## 3.3 NONCLINICAL SAFETY

### 3.3.1 Carcinogenicity

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

### 3.3.2 Genotoxicity

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

### 3.3.3 Impairment of Fertility

No fertility studies or reproductive toxicity testing of Vabysmo have been conducted. In a 6-month cynomolgus monkey study with faricimab doses of up to 3mg/eye (10x clinical exposures based on AUC), no treatment-related changes were noted in reproductive organs in male or female animals that denote adverse effects on fertility.

### 3.3.4 Reproductive toxicity

VEGF inhibition has been shown to cause malformations, embryo-fetal resorption, and decreased fetal weight. VEGF inhibition has also been shown to affect follicular development, corpus luteum function, and fertility. No dedicated studies addressing the effects of Ang-2 inhibition on pregnancy are available. Based on non-clinical information Ang-2 inhibition may lead to effects comparable to VEGF inhibition. Systemic exposure after ocular administration of Vabysmo is very low.

No effects on 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. The no observed adverse effect level (NOAEL) was determined to be 3 mg/kg, the highest dose tested (523 times the clinical exposure based on the Cmax at the maximum recommended human dose of a single 6 mg/eye intravitreal dose).

# 4. PHARMACEUTICAL PARTICULARS

## 4.1 STORAGE

Shelf life: As registered locally

Store in a refrigerator (2°C to 8°C)

Do not freeze.

Keep the vial or sealed tray containing the pre-filled syringe in the original carton to protect from light.

Prior to use, the unopened vial or sealed tray containing the pre-filled syringe may be kept at room temperature, 20°C to 25°C (68°F to 77°F), in the original carton, 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.

## 4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

*Preparation for Administration*

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

Do not shake.

Vabysmo should be inspected visually upon removal from the refrigerator and prior to administration. Do not use if particulates, cloudiness, or discoloration are visible. Do not use if the packaging, vial, transfer filter needle, pre-filled syringe or injection filter needle are damaged or expired.

The contents of the vial and pre-filled syringe are sterile and for single use only.

Use aseptic technique for preparation of the intravitreal injection.

*Instructions for administration*
See section 2.2 Dosage and Administration for dosing instructions.

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

*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.

## 4.3 PACKS

One pack contains one vial (Type 1 glass vial with butyl rubber stopper, aluminium seal and flip-off cap) and one transfer filter needle.

**Medicine: keep out of reach of children**

Current at December 2025

Roche F. Hoffmann-La Roche Ltd, Basel, Switzerland

## Instructions For Use of Vial - Preparation for Administration

Before you start:

- Read all the instructions carefully before using Vabysmo.
- The Vabysmo kit includes a glass vial and transfer filter needle. The glass vial is for a single dose only. The filter needle is for single use only.
- Vabysmo should be stored refrigerated at temperatures between 2ºC and 8ºC (36ºF and 46ºF).
  **Do not** freeze.
  **Do not** shake.
- Allow Vabysmo to reach room temperature, 20°C to 25°C (68°F to 77°F) before proceeding with the administration. Keep the vial in the original carton to protect from light.
- The Vabysmo vial may be kept at room temperature for up to 24 hours.
- The Vabysmo vial should be inspected visually prior to administration. Vabysmo is a clear to opalescent and colorless to brownish-yellow liquid solution.
  **Do not** use if particulates, cloudiness, or discoloration are visible.
  **Do not** use if the packaging, vial and/or transfer filter needle are expired, damaged, or have been tampered with (see **Figure A**).
- Use aseptic technique to carry out the preparation of the intravitreal injection.

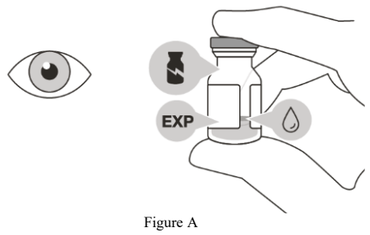



Figure A

**1**. Gather the following supplies:

- One Vabysmo vial (included)
- One sterile 5-micron blunt transfer filter needle 18-gauge x 1½ inch (included)
- One sterile 1 mL Luer lock syringe with a 0.05 mL dose mark (**not included**)
- One sterile injection needle 30-gauge x ½ inch (**not included**)
  **Note** that a 30-gauge injection needle is recommended to avoid increased injection forces that could be experienced with smaller diameter needles.
- Alcohol swab (not included**).**

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

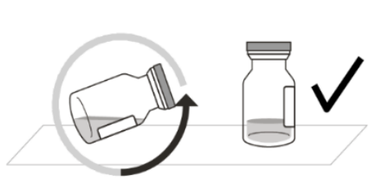


Figure B

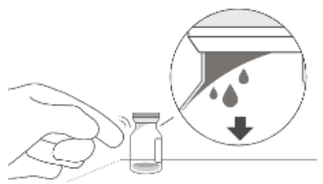


Figure C

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

Figure D

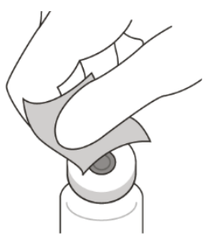


Figure E

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

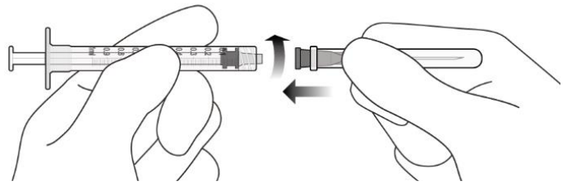


Figure F

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

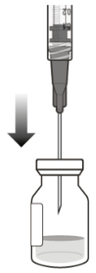


Figure G

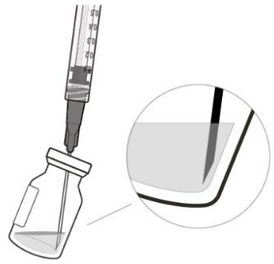


Figure H

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

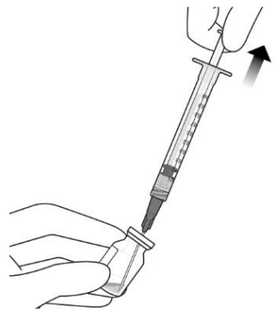


Figure I

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

**8**. Disconnect the transfer filter needle from the syringe and dispose of it in accordance with local regulations.
**Do not use the transfer filter needle for the intravitreal injection.**

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

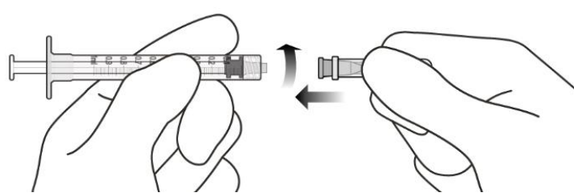


Figure J

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

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

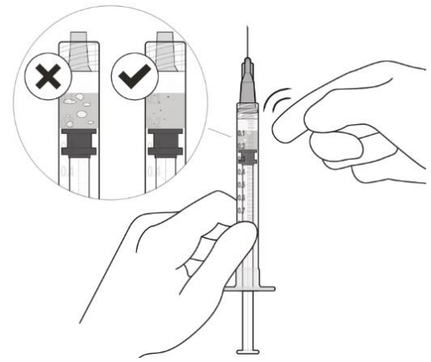


Figure K

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

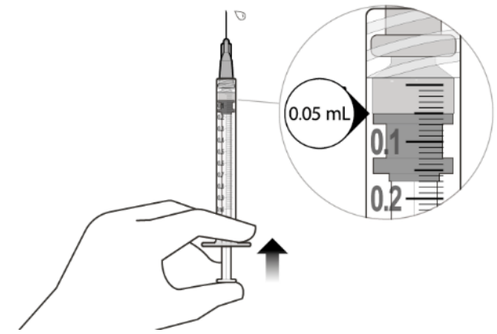



Figure L

## Instructions For Use – Injection Procedure

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

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

# Instructions For Use of Pre-filled Syringe

Before you start:

- Read all the instructions carefully before using Vabysmo.
- The Vabysmo carton includes:
  - A sterile pre-filled syringe in a sealed tray. The pre-filled syringe is for a single dose only.
  - A sterile, 30-gauge x ½ inch, ETW (Extra Thin Wall) injection filter needle with an integrated filter in the hub. The injection filter needle is for single use only.

**Only use the provided injection filter needle for the administration**,
as it was designed to ensure safe ophthalmic use of the medicinal product.

- Vabysmo should be refrigerated at temperatures between 2ºC and 8ºC (36ºF and 46ºF).
  **Do not** freeze.
- Allow Vabysmo to reach room temperature, 20°C to 25°C (68°F to 77°F) before proceeding with the administration.
- Prior to use, keep the sealed tray in the original carton to **protect the pre-filled syringe from light**. The pre-filled syringe may be kept at room temperature in the original carton for up to **24 hours.**
- Vabysmo should be inspected visually prior to administration.
  **Do not** use if the carton seals have been tampered with.
  **Do not** use if the packaging, pre-filled syringe, injection filter needle is expired, damaged, or have been tampered with.
  **Do not** use if the injection filter needle is missing.
  **Do not** remove the finger grip from the syringe.
  **Do not** use if the syringe cap is detached from the Luer lock.
  **Do not** use if particulates, cloudiness, or discoloration are visible. Vabysmo is a clear to opalescent and colorless to brownish-yellow liquid solution.

Carton contents

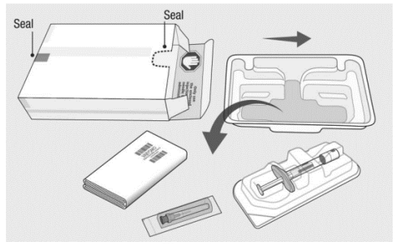



Figure A

Device description

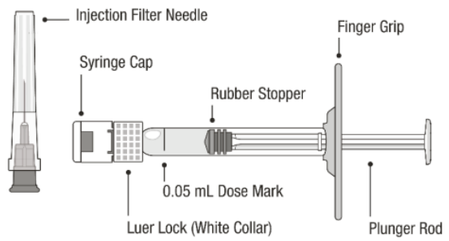



Figure B

Removal of the syringe from the syringe tray (step 1) and all subsequent steps should be done using aseptic technique.

**Note: the dose must be set to the 0.05 mL dose mark.**

**Open tray and remove syringe cap**

**1.** Peel the lid off the syringe tray and aseptically remove the pre-filled syringe.

**2**. Hold the syringe by the white collar; snap off the syringe cap (**see Figure C).**

**Do not** twist off the cap.

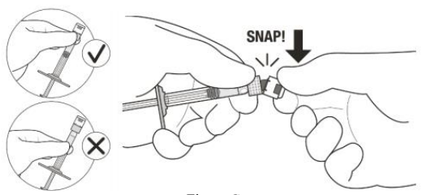



Figure C

**Attach injection filter needle**

**3**. Aseptically remove the injection filter needle from its packaging.

**4**. Aseptically and firmly attach the injection filter needle onto thet syringe Luer lock, (**see Figure D**).

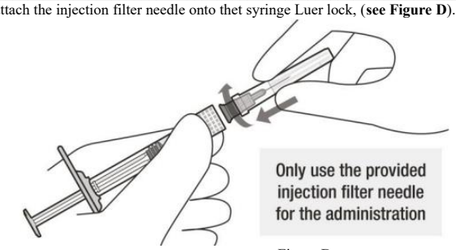



Figure D

5. Carefully remove the needle cap by putting it straight off.

**Dislodge air bubbles**

**6**. Hold the syringe with the injection filter needle pointing up. Check the syringe for air bubbles.

**7**. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (**see Figure E**).

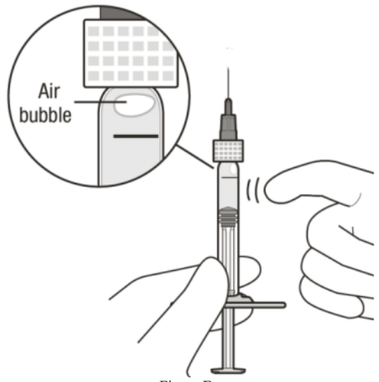



Figure E

**Adjust medicinal product dose and expel air**

**8**. Hold the syringe at eye level and **slowly** push the plunger rod until the **lower edge of the rubber stopper's dome** is aligned with the 0.05 mL dose mark (**see Figure F**). This will expel the air and the excess solution and set the dose to 0.05 mL.

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

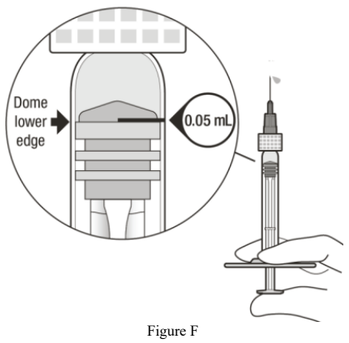



Figure F

# Instructions For Use – Injection Procedure

**9.** The injection procedure should be carried out under aseptic conditions.

Inject **slowly** until the rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL

**Do not** recap or detach the injection filter needle from the syringe. Any unused medicinal product or waste material should be disposed of in accordance with local regulations.