swissmedic

Date: 6 August 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Vabysmo

International non-proprietary name: faricimab

Pharmaceutical form: solution for injection

Dosage strength(s): 6 mg/0.05 mL

Route(s) of administration: intravitreal

Marketing authorisation holder: Roche Pharma (Schweiz) AG

Marketing authorisation no.: 68395

Decision and decision date: extension of therapeutic indication approved on 11 July 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Work-sharing procedure
The applicant requested a work-sharing procedure with the United Kingdom, Canada, Singapore, Australia, and Switzerland.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), and Swissmedic - and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least 2 jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of macular oedema due to retinal vein occlusion (branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO)).

2.2.2 Approved indication

Treatment of macular oedema secondary to retinal vein occlusion (branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO)).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended Vabysmo dose is 6 mg (0.05 mL) for intravitreal injection at 4-week intervals (approximately every 28 ± 7 days or once monthly). Three or more consecutive monthly injections may be required until maximum visual acuity is achieved and/or signs of disease activity are no longer evident. Treatment may then be individualised with extension of the dosing interval as part of a treat-and-extend-scheme. If central subfield thickness (CST) and/or visual acuity deteriorate, the treatment interval may be reduced again accordingly.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	24 August 2023
Formal control completed	5 October 2023
List of Questions (LoQ)	2 February 2024
Response to LoQ	24 March 2024
Preliminary decision	17 May 2024
Response to preliminary decision	2 June 2024
Final decision	11 July 2024
Decision	approval

3 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable since there are no changes with regard to posology and method of administration.
Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment. From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

4 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

5 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

6 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Vabysmo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the “Undesirable effects“ section for advice on the reporting of adverse reactions.

Vabysmo®

Composition

Active substances

Faricimabum (genetically produced in CHO [Chinese Hamster Ovary] cells).

Excipients

L-histidinum, acidum aceticum, L-methioninum, polysorbatum 20 (manufactured from genetically modified maize), natrii chloridum, saccharum (manufactured from genetically modified sugar beet), aqua ad iniectabile.

One single-dose (0.05 mL solution for injection) contains 0.028 mg sodium.

Pharmaceutical form and active substance quantity per unit

Solution for injection in a vial for intravitreal use.
One mL Vabysmo solution for injection contains 120 mg faricimab (120 mg/mL).
Vabysmo solution for injection is a clear to opalescent, colorless to brownish-yellow solution in a single-dose glass vial, containing 28.8 mg faricimab in 0.24 mL solution. This provides a usable quantity for injection of 0.05 mL solution containing 6 mg of faricimab as a single dose.

Indications/Uses

Treatment of neovascular (wet) age-related macular degeneration (nAMD).

Treatment of diabetic macular edema (DME).

Treatment of macular edema secondary to retinal vein occlusion (branch retinal vein occlusion BRVO and central retinal vein occlusion CRVO).

Dosage/Administration

General

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

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

The recommended dose for Vabysmo is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, or once a month) for the first 4 doses. Thereafter, treatment may be individualised using a treat-and-extend approach. Based on the physician's judgment of the individual patient's central retinal thickness (*central subfield thickness*, CST) and/or visual acuity, the dosing interval may be extended up to a maximum of every 16 weeks (4 months). The treatment interval is to be shortened accordingly in the event of deterioration in the CST and/or visual acuity (see section "Properties/Effects, Pharmacodynamics").
Some patients may require injections every 4 weeks (approximately every 28 ± 7 days, or once a month).
Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion.

Diabetic macular edema (DME)

The recommended dose for Vabysmo is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days ± 7 days, or once a month) for the first 4 doses. Thereafter, treatment may be individualised using a treat-and-extend approach. Based on the physician's judgement of the individual patient's CST and/or visual acuity, the dosing interval may be extended up to a maximum of every 16 weeks (4 months). The treatment interval is to be shortened accordingly in the event of deterioration in the CST and/or visual acuity (see section "Properties/Effects, Pharmacodynamics").
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.

Macular edema secondary to retinal vein occlusion (BRVO and CRVO)
The recommended dose for Vabysmo is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days ± 7 days, or once a month); three or more consecutive, monthly injections may be needed, until maximum visual acuity is achieved and/or no signs of disease activity are seen. Thereafter, treatment may be individualised using a treat-and-extend approach. Based on the physician's judgement of the individual patient's CST and/or visual acuity, the dosing interval may be extended. The treatment interval is to be shortened accordingly in the event of deterioration in the CST and/or visual acuity and any renewed extension to the treatment interval after stabilisation must be weighed up carefully (see section "Properties/Effects, Pharmacodynamics"). Treatment intervals longer than 4 months between injections have not been studied.
Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion, but there is no requirement for monthly monitoring between injections.

To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

Duration of treatment

Vabysmo is intended for long-term treatment.

Dose adjustment following undesirable effects/interactions

No dose modifications of Vabysmo are recommended.

Patients with hepatic disorders

No specific studies have been conducted with Vabysmo in patients with hepatic disorders (see “Pharmacokinetics, Kinetics in specific patient groups”).

However, no dose adjustment is required in patients with hepatic disorders.

Patients with renal disorders

No specific studies have been conducted with Vabysmo in patients with renal disorders (see “Pharmacokinetics, Kinetics in specific patient groups”).

However, no dose adjustment is required in patients with renal disorders.

Elderly patients

In the six phase III clinical studies, approximately 58% (1496/2571) of patients randomized to receive treatment with Vabysmo were aged ≥ 65 years. Population pharmacokinetic analysis has shown an effect of age on ocular pharmacokinetics of faricimab. However, the effect was not considered clinically meaningful. No significant differences in the efficacy or safety of faricimab were determined with increasing age in these studies. No dose adjustment is required in patients aged ≥ 65 years (see “Pharmacokinetics, Kinetics in specific patient groups”).

Children and adolescents

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

Special patient groups

No special dose adjustments are required for any of the populations that have been studied (e.g., in older patients or based on gender or ethnic origin).

Delayed administration

If an injection is delayed or missed, the patient should return to be assessed by physician at the next available visit and treatment is then to be continued at the physician’s discretion.

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

Mode of administration

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

Immediately after 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 in the event it is required.

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

Comprehensive instructions for the administration of Vabysmo are given in the Instructions for Use (see “Instructions for Use”).

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 a rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

Warnings and precautions

Intravitreal injection-related reactions

Intravitreal injections, including those with Vabysmo have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tears and iatrogenic traumatic cataracts. 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 that are suggestive of endophthalmitis, or any of the above-mentioned events without delay, to permit prompt and appropriate management.

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injections, including those with Vabysmo. Special precautions are required 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 appropriately and treated as necessary.

Systemic effects

Systemic adverse events, including arterial thromboembolic events, have been reported and there is a theoretical risk that these may be related to VEGF inhibition. A low incidence of arterial thromboembolic events was observed in the faricimab clinical trials in patients with nAMD, DME, BRVO and CRVO.

Immunogenicity

The active substance in Vabysmo is a therapeutic protein. An immunological reaction to Vabysmo is therefore possible. Patients should be instructed to report any signs or symptoms of intraocular inflammation such as loss of vision, 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 have not been studied.

Concomitant use of other anti-VEGF medicinal products

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

Interrupting treatment

Treatment should initially be interrupted in patients with:

- rhegmatogenous retinal detachment, stage 3 or 4 macular holes, retinal tears; treatment should not be resumed until an adequate repair has been performed.
- a 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 any earlier than the next scheduled appointment for treatment.
- performed or planned intraocular surgery within the previous or next 28 days; treatment should not be resumed any earlier than the next scheduled appointment for treatment.

Retinal pigment epithelial tear

Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for nAMD include a large and/or high pigment epithelial detachment. When initiating Vabysmo therapy, caution should therefore be exercised in patients with these risk factors for retinal pigment epithelial tears.

Populations with limited data

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

Drug abuse and dependence

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

Other information

Vabysmo solution for injection for intravitreal use contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially “sodium-free“.

Interactions

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

Pregnancy, lactation

Women of childbearing age

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

Pregnancy

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

No adverse reactions were observed in a study conducted on pregnant cynomolgus monkeys (see “Preclinical data, 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 data, Ang-2 inhibition may lead to effects comparable to those of VEGF inhibition. Systemic exposure is very slow after ocular administration of Vabysmo.

It is not known whether faricimab can cross the placenta or cause harm to the unborn child when administered to pregnant women. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity and to embryo-fetal development. Although the systemic exposure after ocular administration is very low, faricimab should not be used during pregnancy unless treatment is required due to the clinical condition of the woman.

Birth process

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

Lactation

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

Fertility

No reproductive or fertility studies have been conducted. No effects on reproductive organs were observed in a 6-month study conducted on cynomolgus monkeys at faricimab doses of up to 3 mg/eye (8-10 x the clinical exposures based on AUC). 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.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile from clinical studies

The following safety data are derived from actively controlled (aflibercept) phase III studies.

A total of 4489 patients constituted the safety population in the six phase III clinical studies (2567 patients treated with Vabysmo; 664 with nAMD, 1262 with DME and 641 with BRVO and CRVO). The most serious adverse reactions were serious cataracts (0.8%), uveitis (0.5%), endophthalmitis (0.4%), vitritis (0.4%), retinal tears (0.2%), rhegmatogenous retinal detachment (0.1%) and traumatic cataract (<0.1%).

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

List of adverse reactions

The safety data described below include all adverse reactions from the six phase III clinical studies in the indications nAMD, DME, BRVO and CRVO, as well as from post-marketing surveillance, with a justifiable possibility of attributing causality to the injection procedure or medicinal product. The adverse reactions are listed according to the MedDRA system organ class and ranked by frequency using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and not known (frequency cannot be estimated from the available data).

Table 1: Summary of adverse reactions

Adverse reactions	Vabysmo N = 2567	Frequency category
Eye Disorders		
Cataract	9.7%	Common
Conjunctival hemorrhage	6.7%	Common
Vitreous detachment	4.2%	Common
Increased intraocular pressure	3.5%	Common
Vitreous opacities	3.5%	Common
RPE tear (nAMD only)	2.9%	Common
Eye pain	2.5%	Common
Corneal abrasion	0.9%	Uncommon
Eye irritation	0.8%	Uncommon
Increased lacrimation	0.8%	Uncommon
Eye pruritus	0.7%	Uncommon
Ocular discomfort	0.7%	Uncommon

Ocular hyperemia	0.7%	Uncommon
Blurred vision	0.7%	Uncommon
Iritis	0.6%	Uncommon
Reduced visual acuity	0.6%	Uncommon
Uveitis	0.5%	Uncommon
Endophthalmitis	0.4%	Uncommon
Sensation of foreign body	0.4%	Uncommon
Vitreous hemorrhage	0.4%	Uncommon
Vitritis	0.4%	Uncommon
Iridocyclitis	0.3%	Uncommon
Conjunctival hyperemia	0.2%	Uncommon
Procedural pain	0.2%	Uncommon
Retinal tear	0.2%	Uncommon
Rhegmatogenous retinal detachment	0.1%	Uncommon
Traumatic cataract	<0.1%	Rare
Transient reduction in visual acuity	< 0.1%	Rare
Retinal vasculitis*	-	Not known
Retinal occlusive vasculitis*	-	Not known

* These are adverse reactions that were identified based on spontaneous post-marketing reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Description of specific adverse reactions and additional information

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

Undesirable effects from the post-marketing phase

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

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Doses higher than the recommended dosing regimen have not been studied. Overdosing with a greater injection volume than recommended 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.

Properties/Effects

ATC code

S01LA09

Mechanism of action

Faricimab is a humanized bispecific immunoglobulin G1 (IgG1) antibody that acts through inhibition of two distinct signalling pathways by neutralization of both Ang-2 (angiopoietin-2) and VEGF-A (vascular endothelial growth factor A). Ang-2 causes vascular instability by promoting endothelial destabilization, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitizes blood vessels to the activity of VEGF-A, resulting in further vascular destabilization. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularization. Through dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability.

Pharmacodynamics

In the six phase III studies described in the following, a suppression in the median ocular concentrations of free ANG-2 and free VEGF-A was detected from Day 7 compared to baseline.

nAMD
Similar reductions in the mean thickness of the central region of the fovea (central subfield thickness, CST) to those for aflibercept were observed from baseline through week 48 with Vabysmo. The mean CST reduction from baseline to the primary endpoint visits (mean at weeks 40, 44 and 48) was -137 µm and -137 µm for Vabysmo dosed at intervals of 8 weeks (q8w), 12 weeks (q12w) or 16 weeks (q16w) versus -129 µm and -131 µm with the use of aflibercept in the TENAYA and LUCERNE studies, respectively. These mean CST reductions were maintained throughout year 2. Vabysmo and

aflibercept had a comparable effect on the reduction of intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelial detachment (PED). At the primary endpoint visits, the proportion of patients in the TENAYA and LUCERNE studies, respectively, without IRF was 76%-82% and 78%-85 % under treatment with Vabysmo vs 74%-85% and 78%-84% under treatment with aflibercept. The percentage of patients without SRF in the two studies was 70%-79% and 66%-78% under treatment with Vabysmo vs 66%-78% and 62%-76% under treatment with aflibercept. The percentage of patients without PED in the two studies was 3%-8% and 3%-6% under treatment with Vabysmo vs 8%-10% and 7%-9% under treatment with aflibercept. These reductions in IRF, SRF and PED were maintained in year 2 (weeks 104-108).

Comparable changes from baseline in the total area of lesions due to choroidal neovascularisation (CNV) and comparable reductions in CNV leakage area with excretion of blood and fluid were observed in both studies for patients under treatment with Vabysmo and aflibercept at week 48.

DME

Reductions in mean CST from baseline observed in both the YOSEMITE study and the RHINE study were numerically greater in patients treated with Vabysmo every 8 weeks (q8w) and Vabysmo up to q16w adjustable dosing as compared to aflibercept q8w from week 4 to week 100. Greater proportions of patients in both Vabysmo arms achieved absence of IRF and absence of DME (defined as reaching CST below 325 µm on OCT) over time in both studies, compared to the aflibercept arm. Comparable reductions in SRF were observed across the respective Vabysmo and aflibercept treatment arms over time in both studies. The mean reduction of CST from baseline to the primary endpoint visits (averaged at weeks 48, 52 and 56) in the YOSEMITE study was 207 µm and 197 µm in patients treated with Vabysmo q8w and Vabysmo up to q16w adjustable dosing compared to 170 µm in patients treated with aflibercept q8w; results were 196 µm, 188 µm and 170 µm, respectively in the RHINE study. These mean CST reductions were maintained through year 2. The proportions of patients with absence of DME at primary endpoint visits (min-max) in the YOSEMITE study were 77%-87% and 80%-82% in patients treated with Vabysmo q8w and Vabysmo up to q16w adjustable dosing, respectively, as compared to 64%-71% in patients treated with aflibercept q8w; results were 85%-90%, 83%-87%, and 71%-77%, respectively in the RHINE study. These results were maintained through year 2.

In the YOSEMITE study, the proportions of patients with absence of IRF at primary endpoint visits (averaged at weeks 48, 52 and 56) were 42%-48% and 34%-43% in patients treated with Vabysmo q8w and Vabysmo up to q16w adjustable dosing, respectively, as compared to 22%-25% in patients treated with aflibercept q8w; results were 39%-43 %, 33%-41%, and 23%-29%, respectively in the RHINE study. These results were maintained through year 2.

BRVO and CRVO

In phase III studies in patients with branch retinal vein occlusion (BRVO; BALATON) and central/hemiretinal vein occlusion (C/HRVO; COMINO), reductions in mean CST were observed from baseline to week 24 with Vabysmo every 4 weeks (q4w) and were comparable to those seen with aflibercept q4w. The mean CST reduction from baseline to week 24 was 311.4 µm for Vabysmo q4w versus 304.4 µm for aflibercept q4w, and 461.6 µm for Vabysmo q4w versus 448.8 µm for aflibercept q4w, in BALATON and COMINO, respectively. CST reductions were maintained through week 72 when patients moved to a Vabysmo up to q16w adjustable dosing regimen.

Comparable proportions of patients in both Vabysmo and aflibercept arms achieved absence of IRF, absence of SRF and absence of macular edema (defined as reaching CST below 325 µm) over time through week 24, in both studies. These results were maintained through week 72 when patients moved to a Vabysmo up to q16w adjustable dosing regimen.

In BALATON, at week 24, the proportion of patients with absence of macular edema was 95.3% in patients treated with Vabysmo q4w versus 93.9% in patients treated with aflibercept q4w; the proportion of patients with absence of IRF was 72.5% in patients treated with Vabysmo q4w versus 66% in patients treated with aflibercept q4w. The proportion of patients with absence of SRF was 91.3% in patients in the Vabysmo q4w arm, versus 90.3% in patients in the aflibercept q4w arm.

In COMINO, at week 24, the proportion of patients with absence of macular edema was 93.7% in patients treated with Vabysmo q4w versus 92% in patients treated with aflibercept q4w. The proportion of patients with absence of IRF was 76.2% in patients treated with Vabysmo q4w versus 70.8% in patients treated with aflibercept q4w; the proportion of patients with absence of SRF was 96.4% in patients treated with Vabysmo q4w versus 93.4% in patients treated with aflibercept q4w.

Clinical efficacy

Treatment of neovascular (wet) age-related macular degeneration (nAMD)

The safety and efficacy of faricimab were evaluated in two 2-arm, randomized (1:1), multicentre, double-masked studies (TENAYA and LUCERNE) in patients with nAMD compared to anti-VEGF treatment. Treatment (faricimab 6 mg or aflibercept 2 mg) was administered by intravitreal injection, initially at 4-week intervals. In the aflibercept arm, the dosing interval after 3 initial aflibercept injections was 8 weeks for the remainder of the study (q8w). In the faricimab arm, the dosing interval was individually adjusted after 4 initial doses. The final (fixed) dosing interval was 8 weeks (q8w), 12 weeks (q12w) or a maximum of 16 weeks (q16w) depending on the change in CST measured using SD-OCT and/or the change in BCVA measured based on ETDRS letter scores, both defined in the protocol, as well as the treating physician’s clinical assessment of the presence/absence of

macular hemorrhage at weeks 20 and 24. From week 60 onwards, patients in the Vabysmo arm were moved to an adjustable dosing regimen, where the dosing interval could be increased by up to 4-week increments (up to q16w) or could be decreased by up to 8 week increments (up to q8w) based on an automated objective assessment of pre-specified visual and anatomical disease activity criteria. Patients in the aflibercept arm remained on q8w dosing throughout the entire study period. Both studies were 112 weeks in duration.

The trials included a total of 1,329 treatment-naïve patients, with 1,135 (85%) patients completing the studies through week 112. A total of 1,326 received at least one dose (664 patients in the faricimab arm). The average age [age range] of the population that was investigated was 75.9 years [50 to 99 years]. The primary efficacy endpoint was the mean change from the baseline in BCVA within the first year (based on the mean over weeks 40, 44 and 48), determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart at a distance of 4 metres. In both studies, the primary hypothesis (non-inferiority) was confirmed: Patients treated with Vabysmo at an interval of up to q16w and patients treated with aflibercept q8w exhibited a comparable mean change in BCVA from their respective baseline at year 1. Meaningful vision gains from baseline were seen through week 112 in both treatment arms. Detailed results for both studies are shown in Tables 2 and 3, as well as in Figure 1 below.

The proportion of patients in the personalised treatment interval groups at week 48 in the TENAYA and LUCERNE studies, respectively, was:

- q16w: 46 %, 45 %
- q12w: 34 %, 33 %
- q8w: 20 %, 22 %

The proportion of patients in the personalised treatment interval groups at week 112 in the TENAYA and LUCERNE, respectively, was:

- q16w: 59%, 67%
- q12w: 15%, 14%
- q8w: 26%, 19%

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

Efficacy outcomes	**TENAYA**	
	Year 1	Year 2

	Vabysmo at intervals of up to q16w N = 334	Aflibercept q8w N = 337	Vabysmo at intervals of up to q16w N = 334	Aflibercept q8w N = 337
Mean change in BCVA from baseline as measured by ETDRS letter score (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)
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%)
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%)

[a] Average of weeks 40, 44 and 48. [b] Average of weeks 104, 108, 112.
BVCA: best corrected visual acuity.
ETDRS: Early Treatment Diabetic Retinopathy Study.
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 the assessment of categorical variables.

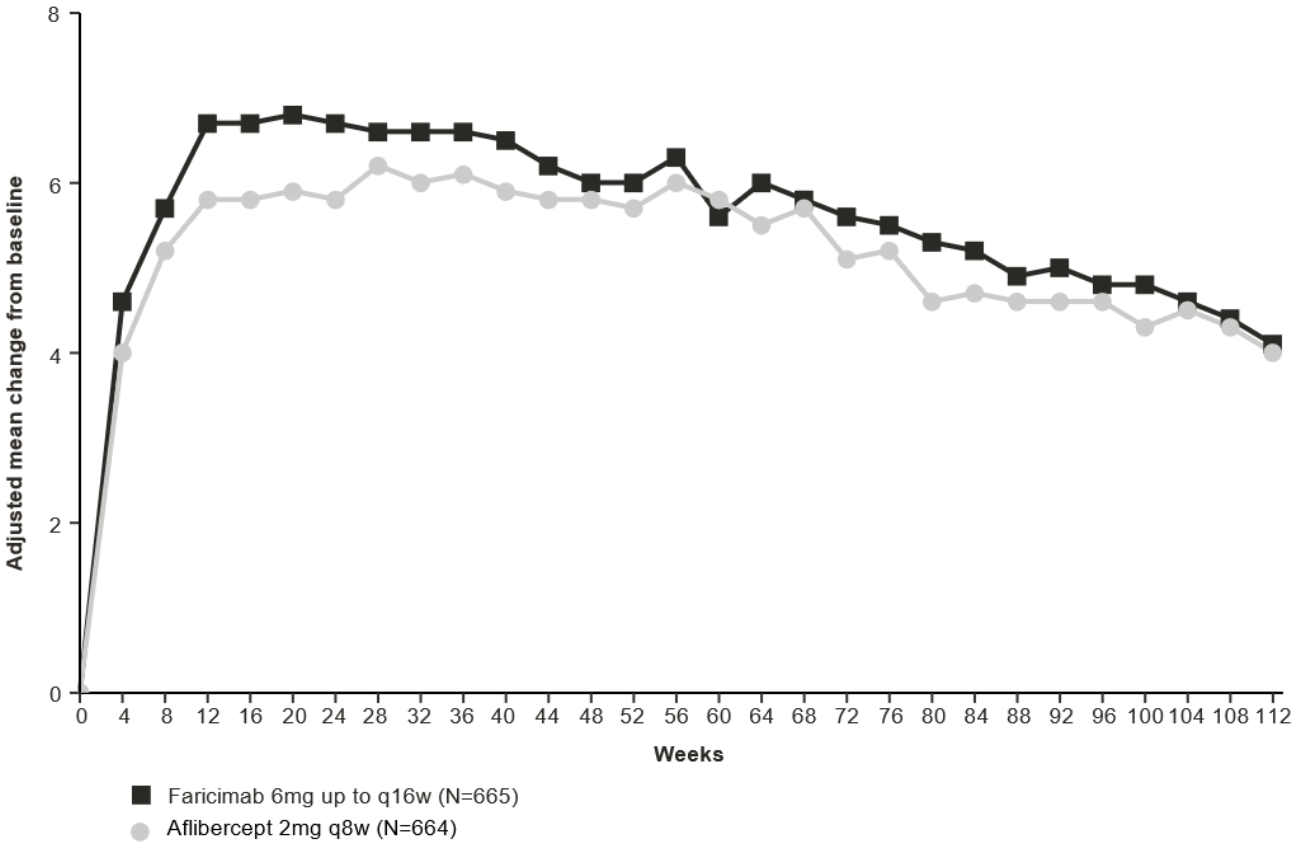
Table 3: Efficacy outcomes at the primary endpoint visits[a] and at year 2[b] in the LUCERNE study

Efficacy outcomes	**LUCERNE**			
	Year 1		Year 2	
	Vabysmo at intervals of up to q16w N = 331	Aflibercept q8w N = 327	Vabysmo at intervals of up to q16w N = 331	Aflibercept q8w N = 327
Mean change in BCVA from baseline as measured by ETDRS letter score (95% CI)	6.6 (5.3, 7,1)	6.6 (5.3, 7.8)	5.0 (3.4, 6.6)	5.2 (3.6, 6.8)
Proportion of patients with ≥ 15 letter gain from baseline	20.2% (15.9%, 24.6%)	22.2% (17.7%, 26.8%)	22.4%	21.3% (16.8%, 25.9%)

(CMH weighted proportion, 95% CI)			(17.8 %, 27.1 %)	
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%)

[a] Average of weeks 40, 44 and 48. [b] Average of weeks 104, 108, 112.
BVCA: best corrected visual acuity.
ETDRS: Early Treatment Diabetic Retinopathy Study.
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 the assessment of categorical variables.

Figure 1: Pooled phase III nAMD studies (TENAYA and LUCERNE): Plot of change from baseline in BCVA in the study eye through week 112: MMRM method (primary estimand) (ITT population)



In both the TENAYA and LUCERNE studies, 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.

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

In both studies, Vabysmo administered at intervals of up to q16w demonstrated clinically meaningful improvements from baseline to week 48 in the National Eye Institute Visual Function Questionnaire (NEI VFQ -25) composite score that were comparable to those for aflibercept q8w. Patients in Vabysmo arms in the TENAYA and LUCERNE studies achieved a ≥ 4-point improvement from baseline in the NEI VFQ -25 composite score at week 48.

Treatment of diabetic macular edema (*DME)*

The safety and efficacy of faricimab were evaluated in two 3-arm, randomized (1:1:1), multicentre, double-masked studies (YOSEMITE and RHINE) conducted over a period of 2 years in patients with DME in comparison to anti-VEGF treatment. Patients in the three study arms received intravitreal injections of 6 mg faricimab q8w (after 6 monthly injections at the start of the treatment), 6 mg faricimab with a personalised injection interval up to a maximum of q16w (after 4 monthly injections at the start of the treatment or 2 mg aflibercept q8w (after 5 monthly injections at the start of the treatment). In the faricimab arm with extended dosing up to q16w, dosing followed a standardized treat-and-extend approach. Based on changes in CST as measured using OCT and/or changes in BCVA as measured with the ETDRS letter score, the personalised injection interval in the faricimab group could be extended by 4 weeks or shortened by 4 or 8 weeks at each of the study drug dosing visits (see “Dosage/Administration“).

The trials included a total of 1,891 patients (of whom approximately 94% had type 2 diabetes mellitus), with 1,622 (85.8%) patients completing the studies through week 100. A total of 1,887 were treated with at least one dose through week 56 (1,262 with Vabysmo). The mean age [age range] of the patients studied was 62.2 years [24 to 91 years]. The study population included both anti-VEGF naïve patients (78%) and patients who had undergone previous anti-VEGF therapy (22%).
The primary efficacy endpoint was the mean change in BCVA from baseline to the end of the first year (mean at weeks 48, 52 and 56) determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart at a distance of 4 metres. In both studies, the primary hypothesis (non-inferiority) was confirmed for both treatment arms: patients treated with Vabysmo q8w or patients treated with Vabysmo on extended dosing up to q16w and patients treated with aflibercept q8w exhibited a comparable mean change from their respective baselines in BCVA at year 1, and these vision gains were maintained through year 2.

After 4 initial monthly doses, the patients in the Vabysmo arm with up to q16w adjustable dosing interval could have received a total of at least 6 and a maximum of 21 injections through week 96. At week 52, 74% and 71%, respectively of patients in the respective Vabysmo arms with up to q16w adjustable dosing in the YOSEMITE and RHINE studies achieved a dosing interval of q16w or q12w (53% and 51% on q16w, 21% and 20% on q12w). Of these patients in the YOSEMITE and RHINE studies, respectively, 75% and 84% maintained ≥ q12w dosing without an interval reduction to 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. At week 96, 78% of patients in the respective Vabysmo arm with up to q16w adjustable dosing achieved a q16w or q12w dosing interval in both studies (60% and 65% on q16w, 18% and 14% on q12w). In 4% and 6% of patients in the YOSEMITE and RHINE studies, respectively, the interval was extended to q8w and the patients maintained a dosing interval of ≤ q8w through week 96; 3% and 5% were only given a q4w interval up to the end of week 96.

Detailed results from the analyses of the YOSEMITE and RHINE studies are given in Tables 4, 5, 6, 7 and in Figure 2 below.

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

Efficacy outcomes	**YOSEMITE**					
	Year 1			**Year 2**		
	Vabysmo q8w N = 315	Vabysmo at intervals of up to q16w adjustable dosing N = 313	Aflibercept q8w N = 312	Vabysmo q8w N = 315	Vabysmo at intervals of up to q16w adjustable dosing N = 313	Aflibercept q8w N = 312
Mean change in BCVA from baseline as measured by ETDRS letter score (97.5 % CI in year 1 and 95 % in 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)
Proportion of patients who gained at least 15 letters in BCVA from baseline (CMH weighted proportion, 95 % CI in 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%)
Proportion of patients who avoided loss of at least 15 letters in BCVA from baseline (CMH weighted proportion, 95 % CI in 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%)

[a] Average of weeks 48, 52, 56; [b]Mean of weeks 92, 96, 100.
BCVA: best corrected visual acuity.
ETDRS: Early Treatment Diabetic Retinopathy Study.
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 the assessment of categorical variables.
Note: The CMH-weighted % data shown for the aflibercept arm are for the comparison between Vabysmo q8w and aflibercept. However the corresponding CMH-weighted % data for the comparison between Vabysmo with extendable dosing vs aflibercept are similar to the data shown above.
ETDRS-DRSS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale (scale for evaluation of diabetic retinopathy from the Early Treatment Diabetic Retinopathy Study).

Table 5: Proportion of patients with an improvement in the ETDRS-DRSS by ≥ 2 steps in week 52 and week 96 compared to baseline in the YOSEMITE study (evaluable population in relation to DR)

Efficacy outcomes	**YOSEMITE**					
	52 weeks			96 weeks		
	Vabysmo q8w N = 237	Vabysmo at intervals of up to q16w adjustable dosing N = 242	Aflibercept q8w N = 229	Vabysmo q8w N = 220	Vabysmo at intervals of 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%

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 the assessment of categorical variables.
Note: The CMH-weighted % data shown for the aflibercept arm are for the comparison between Vabysmo q8w and aflibercept. However the corresponding CMH-weighted % data for the comparison between faricimab with extendable dosing vs aflibercept are similar to the data shown above.

Table 6: Efficacy outcomes at the year 1[a] and year 2[b] primary endpoint visits in the RHINE study

Efficacy outcomes	RHINE					
	Year 1			Year 2		
	Vabysmo q8w N = 317	Vabysmo at intervals of up to q16w adjustable dosing N = 319	Aflibercept q8w N = 315	Vabysmo q8w N = 317	Vabysmo at intervals of up to q16w adjustable dosing N = 319	Aflibercept q8w N = 315
Mean change in BCVA from baseline as measured by ETDRS letter score (97.5 % CI in year 1 and 95 % in 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)
Proportion of patients who gained at least 15 letters in BCVA from baseline (CMH weighted proportion, 95 % CI in 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%)
Proportion of patients who avoided loss of at least 15 letters in BCVA from baseline (CMH weighted proportion, 95 % CI in 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%)

[a] Average of weeks 48, 52, 56; [b]Average of weeks 92, 96, 100.

BVCA: Best Corrected Visual Acuity.

ETDRS: Early Treatment Diabetic Retinopathy Study.

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: The CMH-weighted % data shown for the aflibercept arm are for the comparison between Vabysmo q8w and aflibercept, however the corresponding CMH-weighted % for Vabysmo adjustable vs. aflibercept comparison is similar to the one shown above.

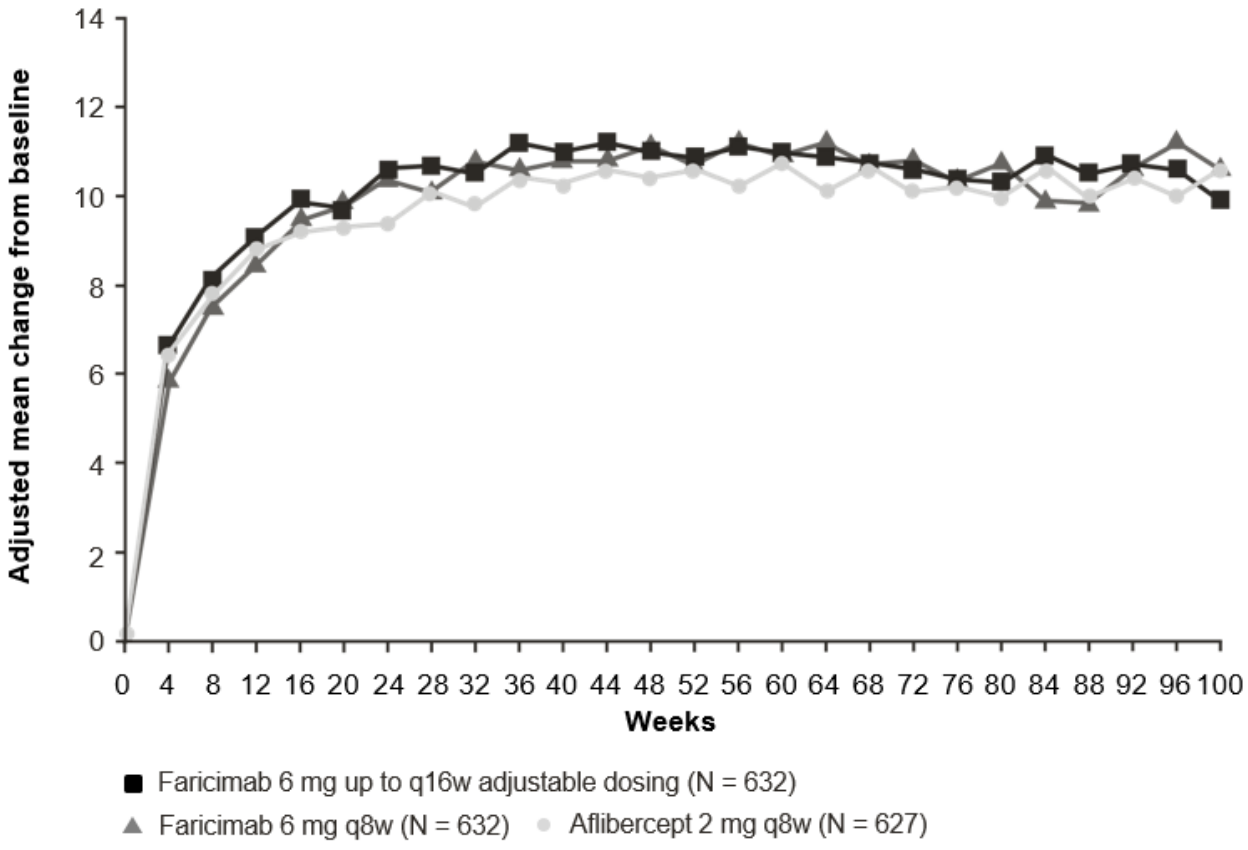
ETDRS-DRSS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale (Scale for evaluation of diabetic retinopathy from the Early Treatment Diabetic Retinopathy Study).

Table 7: Proportion of patients with an improvement in the ETDRS-DRSS by ≥ 2 steps in week 52 and week 96 compared to baseline in the RHINE study (evaluable population in relation to DR)

Efficacy outcomes	RHINE					
	52 weeks			96 weeks		
	Vabysmo q8w N = 231	Vabysmo at intervals of up to q16w adjustable dosing N = 251	Aflibercept q8w N = 238	Vabysmo q8w N = 214	Vabysmo at intervals of 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%

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 the assessment of categorical variables.
Note: The CMH-weighted % data shown for the aflibercept arm are for the comparison between Vabysmo q8w and aflibercept. However the corresponding CMH-weighted % data for the comparison between Vabysmo with extendable dosing vs aflibercept are similar to the data shown above.

Figure 2: Pooled phase III DME studies (YOSEMITE and RHINE): Plot of change from baseline in BCVA in the study eye through week 100: MMRM method (primary estimand) (ITT population)



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

The treatment effect was independent of glycaemic management, and comparable outcomes were achieved with faricimab treatment in patients whose HbA1c improved or worsened by > 0.5 % over time, or remained within 0.5% of baseline.

Treatment of Macular Edema Secondary to BRVO and CRVO

The safety and efficacy of faricimab was investigated in two multicentre studies in patients with macular oedema resulting from BRVO (BALATON) or C/HRVO (COMINO). Both studies consisted of an initial 24-week, randomized (1:1), actively controlled (aflibercept) treatment phase. After this, all patients (including those originally treated with aflibercept) were treated with faricimab based on an individually tailored dosage regimen up to week 68 (last visit in week 72). The dosing interval could be extended by 4 weeks up to a maximum of q16w and then shortened again by 4, 8 or 12 weeks, if necessary (deterioration in CST and/or visual acuity), based on disease activity (assessed using an automated objective evaluation of criteria relating to vision and anatomical criteria defined beforehand). The treatment interval was not extended again after stabilisation of disease activity in patients who required a shortening of the interval. This excluded patients with a minimum (4-week) interval between injections.

A total of 1282 patients (553 in BALATON and 729 in COMINO) were enrolled in the two studies, with 1276 patients treated with at least one dose through week 24 (641 with Vabysmo).

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.

Between week 24 and week 68, 81.5% and 74.0% of the patients receiving Vabysmo 6 mg up to q16w adjustable dosing regimen achieved a q16w or q12w dosing interval in BALATON and COMINO, respectively. Of these patients, 72.1% and 61.6% completed at least one cycle of q12w, and maintained q16w or q12w dosing interval without an interval reduction below q12w through week 68 in BALATON and COMINO, respectively; 1.2% and 2.5% of the patients received only q4w dosing through week 68 in BALATON and COMINO, respectively.

Detailed results of both studies are shown in Table 8 and 9, Figure 3 and Figure 4 below.

Table 8: Efficacy outcomes at the week 24 primary endpoint visits and at the end of the study in BALATON

Efficacy Outcomes	BALATON			
	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
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)
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%)

[a]Average of weeks 64, 68, 72.

BCVA: Best Corrected Visual Acuity

ETDRS: Early Treatment Diabetic Retinopathy Study

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.

Table 9: Efficacy outcomes at the week 24 primary endpoint visits and at the end of the study-COMINO

Efficacy Outcomes	COMINO			
	24 Weeks		72 Weeks[a]	
	Vabysmo N = 366	Aflibercept N = 363	Vabysmo q4w to Vabysmo Adjustable N = 366	Aflibercept q4w to Vabysmo Adjustable N = 363
Mean change in BCVA as measured by ETDRS letter score from baseline (95% CI)	16.9 (15.4, 18.3)	17.3 (15.9, 18.8)	16.9 (15.2, 18.6)	17.1 (15.4, 18.8)

Proportion of patients with ≥ 15 letter gain from baseline (CMH weighted proportion, 95% CI)	56.6% (51.7%, 61.5%)	58.1% (53.3%, 62.9%)	57.6% (52.8%, 62.5%)	59.5% (54.7%, 64.3%)

[a]Average of weeks 64, 68, 72.

BCVA: Best Corrected Visual Acuity

ETDRS: Early Treatment Diabetic Retinopathy Study

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.

Figure 3: Phase III study BALATON: Plot of change from baseline in BCVA in the study through week 72: MMRM method (primary estimand) (ITT population)

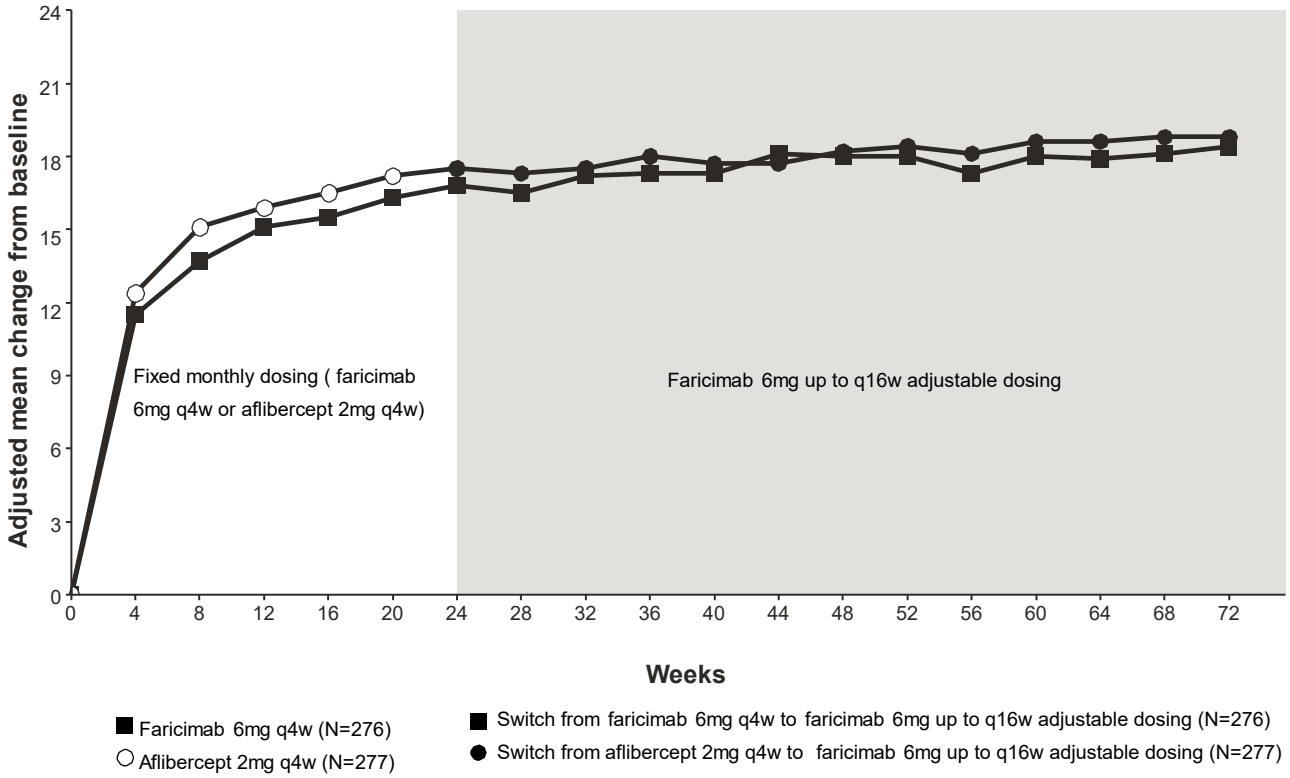
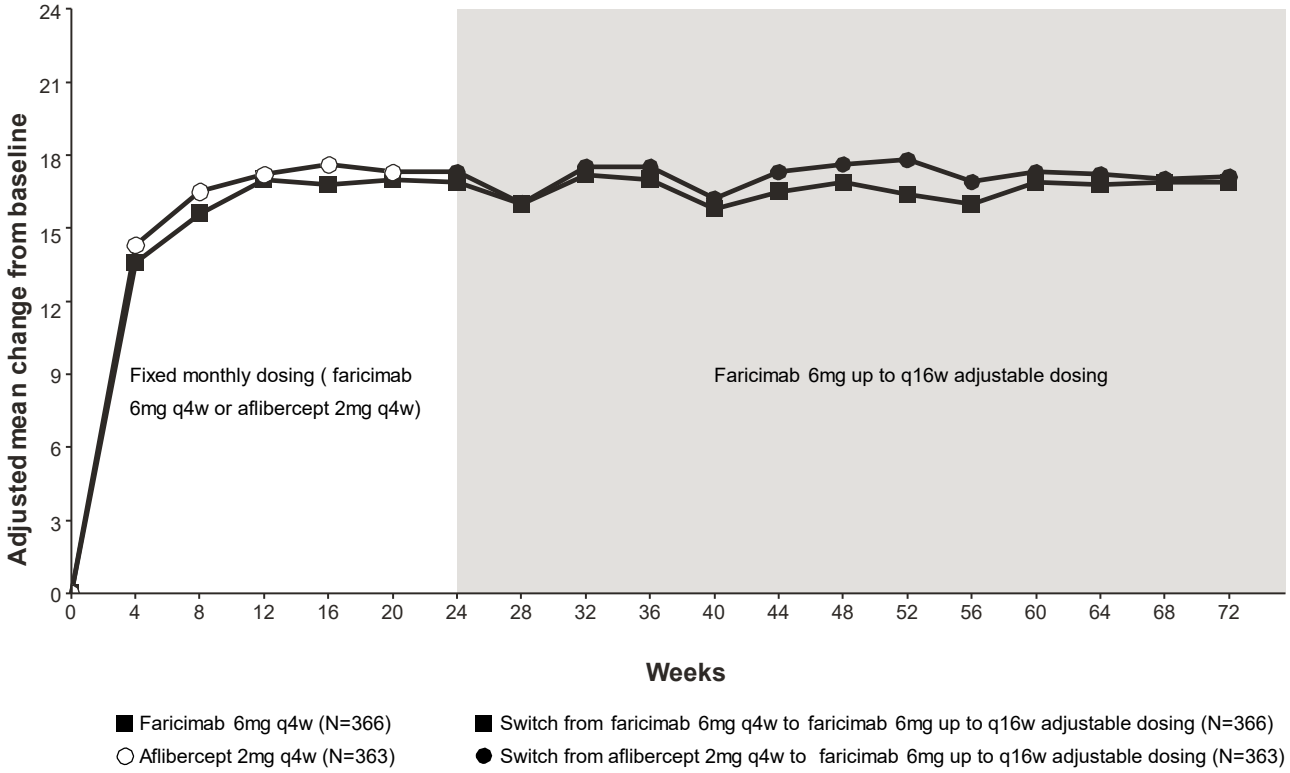


Figure 4: Phase III study COMINO: Plot of change from baseline in BCVA in the study through week 72: MMRM method (primary estimand) (ITT population)



Elderly patients

In the six phase III clinical studies, approximately 58% (1496/2571) of patients randomized to treatment with Vabysmo were aged ≥ 65 years. Population pharmacokinetic analysis has shown an effect of age on the ocular pharmacokinetics of faricimab, which was not considered clinically meaningful (see “Dosage/Administration, Elderly patients“ and “Pharmacokinetics, Elderly patients“).

Paediatrics

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

Further information

Immunogenicity

There is a potential for an immune response in patients treated with Vabysmo (see “Warnings and precautions“).

After dosing with Vabysmo for up to 112 (nAMD), 100 (DME) and 72 (BRVO/CRVO) weeks, treatment-emergent anti-faricimab antibodies were detected in approximately 13.8%, 9.6% and 14.4% of patients with nAMD, DME, and BRVO/CRVO randomized to faricimab, respectively. The clinical significance of anti-faricimab antibodies regarding safety is unclear at this time. Among patients with

anti-faricimab antibodies, a higher incidence of adverse reactions with intraocular inflammation was observed. However, the overall incidence of anti-faricimab antibody positivity and intraocular inflammation in the entire study population is approximately 1%. Anti-faricimab antibodies were not associated with an impact on clinical efficacy or systemic pharmacokinetics.

Pharmacokinetics

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 (C_{max}) are estimated to occur approximately 2 days post-dose. Mean (± SD) free plasma C_{max} are estimated at 0.23 (0.07) µg/mL and 0.22 (0.07) µg/mL respectively in nAMD and in DME patients. After repeated administrations, mean free plasma faricimab trough concentrations are predicted to be 0.002-0.003 µg/mL for q8w dosing.

Faricimab exhibited dose-proportional pharmacokinetics (based on C_{max} and AUC) over the dose range of 0.5 mg-6 mg. There was no accumulation of faricimab in the vitreous body or in plasma following monthly dosing based on exposure estimates from the population pharmacokinetic model.

Pharmacokinetic analysis of patients with nAMD, DME, BRVO and CRVO (N=2977) has shown that the pharmacokinetics of faricimab are comparable in these patients.

Distribution

No information.

Metabolism

The metabolism of faricimab has not been studied directly. Faricimab is assumed to be catabolised into small peptides and amino acids in lysosymes, similar to endogenous IgG molecules.

Elimination

The faricimab plasma concentration-time profile declined in parallel with the concentration-time profiles in the vitreous body and intraocular fluid. The estimated mean ocular half-life and apparent systemic half-life of faricimab are each approximately 7.5 days.

Kinetics in specific patient groups

Hepatic impairment

No formal pharmacokinetic studies have been conducted in patients with hepatic impairment.

Renal impairment

No formal pharmacokinetic studies have been conducted in patients with renal impairment. Pharmacokinetic analysis of patients in all clinical studies including 1115 patients with mild, 669 with moderate and 54 with severe renal impairment, revealed no differences with respect to the systemic pharmacokinetics of faricimab after intravitreal administration of Vabysmo.

Elderly patients

In the six phase III clinical studies, approximately 58% (1496/2571) of patients randomized to treatment with Vabysmo were aged ≥ 65 years. The population pharmacokinetic analysis revealed an effect of age on the ocular pharmacokinetics of faricimab, which was, however, not considered clinically meaningful.

Children and adolescents

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

Other demographic factors

The population pharmacokinetic analysis revealed an effect of body weight on the ocular and systemic pharmacokinetics of faricimab. This effect was not considered clinically meaningful, such that, no dose adjustment is required.

A population-kinetic analysis provides no indication for any influences on the systemic pharmacokinetics of Vabysmo based on ethnic origin or gender.

Preclinical data

Genotoxicity

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

Carcinogenicity

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

Fertility

No effects on reproductive organs were observed in a 6-month cynomolgus monkey study at faricimab doses up to 3 mg/eye (8-10 x clinical exposures based on AUC).

Reproductive toxicity

No effects on pregnancy or fetuses were observed in an embryo-fetal development study conducted in pregnant cynomolgus monkeys given 5 weekly intravenous injections of Vabysmo at 1 mg/kg or 3 mg/kg, starting on day 20 of gestation. Serum exposure (C_{max}) in monkeys at the no observed

adverse effect level (NOAEL) dose of 3 mg/kg was more than 500 times that in humans at a dose of 6 mg given by intravitreal injection once every 4 weeks.

Other information

Preparation for administration
Vabysmo is a sterile, preservative-free, clear to opalescent, colorless to brownish-yellow solution.
Vabysmo should be inspected visually upon removal from the refrigerator and prior to administration.
The vial must not be used if particulates, cloudiness or discoloration are visible.
The contents of the vial and transfer filter needle are sterile and intended for single use only. Do not use if the packaging, vial and/or transfer filter needle are damaged or have expired.
Use an aseptic technique during preparation of the intravitreal injection.

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date (“EXP“) stated on the pack.

Special precautions for storage

Store in a refrigerator at 2-8 °C. Do not shake. Do not freeze.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Prior to use, the unopened vial of Vabysmo 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.

Instructions for handling

See “Dosage/Administration“ for dosing instructions.
For detailed instructions on administration, see “Instructions for Use“.
Disposal of unused/expired medicines

The release of pharmaceuticals into 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.

Authorisation number

68395 (Swissmedic).

Packs

Vabysmo 28.8 mg/0.24 mL, solution for injection in a vial incl. 1 filter needle: 1 [B]

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd, Basel.

Date of revision of the text

May 2024.

Instructions for Use

The following information is intended for healthcare professionals only:

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 contains a single dose only. The filter needle is for single use only.
- Vabysmo should be stored refrigerated at temperatures between 2 °C to 8 °C.

  Do not freeze.

  Do not shake.
- Allow Vabysmo to reach room temperature, 20 °C to 25 °C 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 have been opened, are damaged or have expired. (see **Figure A**).
- Use an aseptic technique to carry out the preparation of the intravitreal injection.

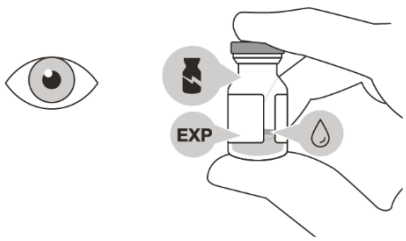


Figure A

Instructions for use of vial:

1. Prepare the following supplies:

- One Vabysmo vial (included)
- One sterile 5-micron blunt transfer filter needle 18-gauge x 1½ inch or approx. 1.2 mm x 40 mm (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 would be necessary with smaller diameter needles.
- Alcohol swab (**not included**).

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

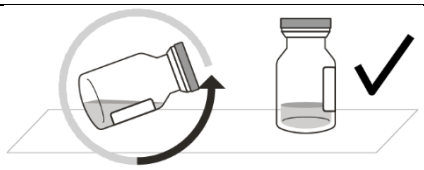


Figure B

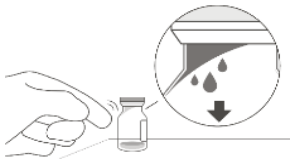


Figure C

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

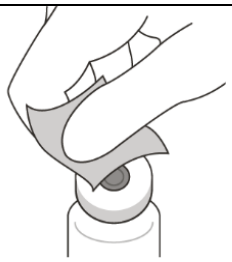


Figure E

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**).

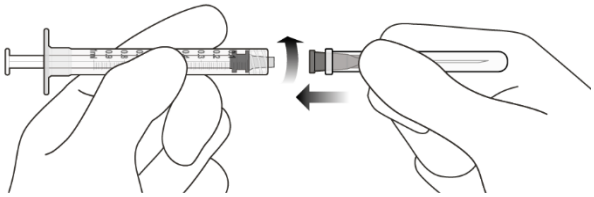


Figure F

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

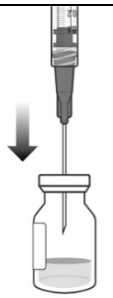


Figure G

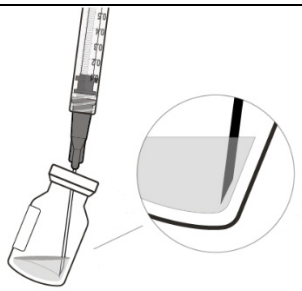


Figure H

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 the introduction of air.

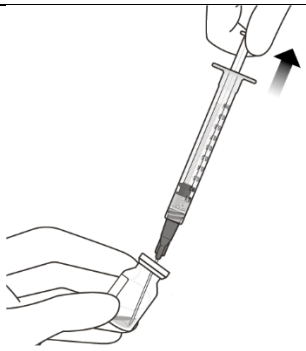


Figure I

7. Ensure that the plunger rod is drawn back sufficiently 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**).

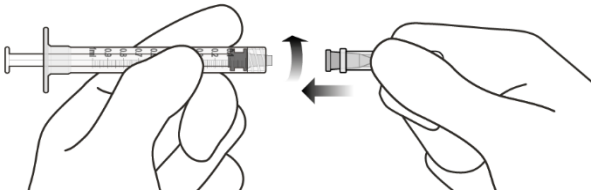


Figure J

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**).

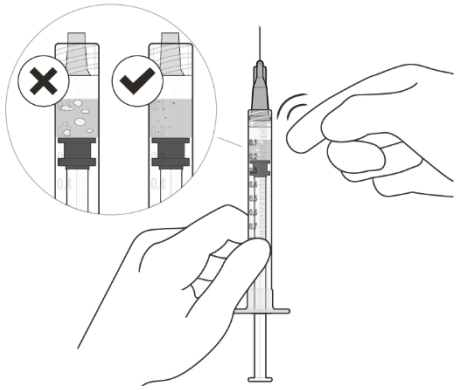


Figure K

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

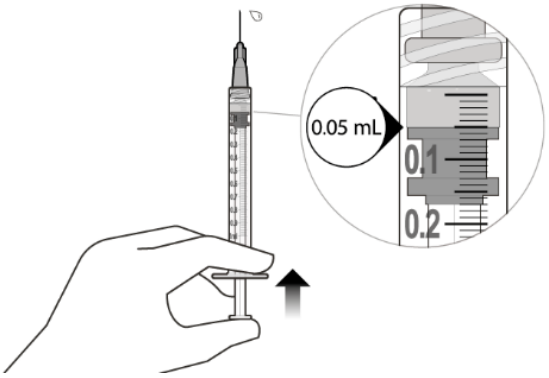


Figure L

13. Inject slowly until the rubber stopper reaches the front 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 front of the syringe barrel after the injection.

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