Summary Report of Benefit-Risk Assessment

VABYSMO SOLUTION FOR INJECTION 6MG/0.05ML

NEW DRUG APPLICATION

Active Ingredient(s)	Faricimab
Product Registrant	Roche Singapore Pte. Ltd.
Product Registration Number	SIN16514P
Application Route	Full evaluation
Date of Approval	16 June 2022

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A INTRODUCTION

Vabysmo is indicated for the treatment of neovascular age-related macular degeneration (nAMD) and visual impairment due to diabetic macular edema (DME).

The active substance, faricimab, is a humanised bispecific immunoglobulin G1 (IgG1) antibody that binds to and inhibits angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A), suppresses endothelial cell proliferation, neovascularisation and vascular permeability and promotes vascular stability.

Vabysmo is available as a solution for injection containing 6 mg/0.05ml of faricimab. Other ingredients in the vial are L-histidine, acetic acid, L-methionine, sodium chloride, sucrose, polysorbate 20 and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, faricimab, is manufactured at Roche Diagnostics GmbH, Penzberg, Germany. The drug product, Vabysmo solution for injection 6mg/0.05ml, is manufactured at F. Hoffmann-La Roche Ltd, Kaiseraugst, Switzerland.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on four consecutive production-scale batches.

The characterisation of the drug substance and its impurities were in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications were established in accordance with ICH Q6B and the impurity limits have been appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support storage of the drug substance at -40^{o}C with a shelf life of 36 months. The packaging consists of 6 L ethylene vinyl acetate single-use bags.

Drug product:
The manufacturing process utilises aseptic processing.

The manufacturing site involved is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B and impurity limits were adequately qualified. The analytical methods used were adequately described and non-

compendial methods have been validated in accordance with ICH guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 30 months when stored at 2-8ºC. Prior to use, the unopened vial may be stored at 20°C to 25°C for up to 24 hours. The container closure system is a Type 1 glass vial with butyl rubber stopper, aluminium seal and flip-off cap.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of faricimab for the treatment of nAMD and DME was based primarily on data from two identically designed pivotal Phase III studies per indication, namely, study GR40306 (TENAYA) and study GR40844 (LUCERNE) for nAMD, and study GR40349 (YOSEMITE) and study GR40398 (RHINE) for DME.

Neovascular Age-related Macular Degeneration (nAMD)

Studies TENAYA and LUCERNE were multicentre, randomised, active comparator-controlled, double-masked, 112-week non-inferiority studies that compared the efficacy, safety and durability of faricimab 6 mg with aflibercept 2 mg in treatment-naïve patients aged ≥50 years with nAMD and who had best corrected visual acuity (BCVA) of 78 to 28 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart.

Patients were randomised in a 1:1 ratio to receive treatment with either faricimab (Arm A) or aflibercept (Arm B). In Arm A (faricimab arm), intravitreal (IVT) faricimab 6 mg was administered every 4 weeks (Q4W) up to Week 12. At Week 20, patients with active nAMD disease based on assessments of visual and anatomic criteria received a faricimab 6 mg dose and then continued to receive 6 mg doses in a fixed 8-weekly (Q8W) regimen until Week 60. At Week 24, patients with active nAMD disease (excluding those with active disease at Week 20) received a faricimab 6 mg dose and then continued to receive faricimab 6 mg every 12 weeks (Q12W) until Week 60. Patients who did not have nAMD active disease at Weeks 20 or 24 were treated with faricimab 6 mg every 16 weeks (Q16W) until Week 60. In Arm B (aflibercept arm), IVT aflibercept 2 mg was administered Q4W up to Week 12, followed by aflibercept 2 mg Q8W up to Week 60.

The primary efficacy endpoint was the change from baseline in BCVA averaged over Weeks 40, 44, and 48, as measured on the ETDRS letter score. To demonstrate non-inferiority of faricimab to aflibercept, the lower bound of the 2-sided 95% confidence interval (CI) for the difference in adjusted mean change from baseline (faricimab minus aflibercept) in BCVA must be greater than -4 letters in the intent-to-treat (ITT) population. The non-inferiority design and non-inferiority margin were considered appropriate. The secondary efficacy endpoints were the change from baseline in BCVA over time, proportion of patients gaining ≥15, ≥10, ≥5 or ≥0 letters from baseline BCVA, proportion of patients with BCVA Snellen equivalent of 20/40 or better, proportion of patients with BCVA Snellen equivalent of 20/200 or worse, change from baseline in central subfield thickness (CST), proportion of patients with absence of intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelial detachment (PED), change from baseline in total area of choroidal neovascularisation (CNV) lesion and change from baseline in total area of leakage.

In Study TENAYA, a total of 671 patients were randomised (Arm A: 334; Arm B: 337) and analysed in the Full Analysis Set. The demographics and baseline disease characteristics of the subjects were well-balanced across the treatment arms. The mean age was 76.3 years (range: 50.0 to 99.0 years), and 417 patients (62.1%) were ≥75 years of age. The majority of patients were female (59.9%) and White (90.2%). The median time since nAMD diagnosis was 0.6 months in the two treatment arms. The mean BCVA and CST values in the study eye at baseline were comparable between faricimab arm and aflibercept arm (BCVA: 61.3 letters vs 61.5 letters; CST: 486.4 µm vs 473.9 µm).

Study LUCERNE randomised and analysed a total of 658 patients (Arm A: 331; Arm B: 327) in the Full Analysis Set. The patient demographics and baseline disease characteristics were well-balanced across the treatment arms. The mean age was 75.5 years (range: 50.0 to 95.0 years), and 371 patients (56.4%) were ≥75 years of age. The majority of patients were female (59.4%) and White (83.3%). The median time since nAMD diagnosis was 0.6 months in faricimab arm and 0.7 months in aflibercept arm. The mean BCVA and CST values in the study eye at baseline were comparable between faricimab arm and aflibercept arm (BCVA: 58.7 letters vs 58.9 letters; CST: 490.3 µm vs 469.6 µm).

Both studies met the primary efficacy endpoint, with the lower bounds of the 95% CI for the adjusted mean difference in BCVA change from baseline to Weeks 40/44/48 between the treatment arms in the ITT population fell within the pre-specified non-inferiority margin of -4 letters (TENAYA: 0.7 letters [95% CI: -1.1, 2.5]; LUCERNE: 0.0 letters [95% CI: -1.7, 1.8]). The mean BCVA change from baseline to Weeks 52/56/60 (TENAYA: 0.7 letters [95% CI: -1.2, 2.7]; LUCERNE: -0.6 letters [95% CI: -2.4, 1.3]) was similar to the result from baseline to Weeks 40/44/48. The results in the per-protocol (PP) populations were consistent with those in the ITT populations from both studies.

The secondary endpoints supported the primary analysis. A comparable proportion of patients in the faricimab and aflibercept arms gained ≥15 letters in BCVA over Weeks 40/44/48 in Study TENAYA (20.0% vs 15.7%) and Study LUCERNE (20.2% vs 22.2%). Similar proportions of patients in faricimab arm and aflibercept arm achieved BCVA Snellen equivalent 20/40 or better over Weeks 40/44/48 in Study TENAYA (56.2% vs 57.3%) and Study LUCERNE (54.6% vs 49.8%). Faricimab treatment showed comparable reductions in CST from baseline over Weeks 40/44/48 relative to aflibercept in Study TENAYA (-136.8 µm vs -129.4 µm) and Study LUCERNE (-137.1 µm vs -130.8 µm). The proportion of patients with an absence of IRF, SRF, or PED through Week 48 was comparable between the treatment arms in the two studies.

Based on a post-hoc analysis, the faricimab dose interval subgroups (Q8W, Q12W and Q16W) showed consistent BCVA gain relative to the overall faricimab arm with overlapping confidence intervals in the mean BCVA gain over Weeks 40/44/48 and Weeks 52/56/60.

Summary of Key Efficacy Results (Studies TENAYA and LUCERNE) – ITT Population

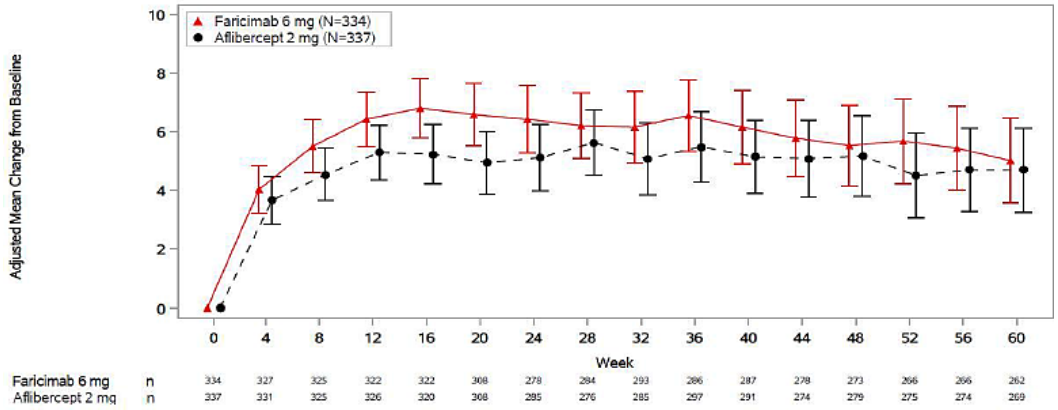
	Study TENAYA study		**Study LUCERNE**	
	Faricimab (N = 334)	**Aflibercept (N = 337)**	**Faricimab (N = 334)**	**Aflibercept (N = 327)**
Primary endpoint - BCVA change from baseline averaged over Weeks 40/44/48 (ETDRS letter score)				
Adjusted mean change (95% CI)	5.8 (4.6, 7.1)	5.1 (3.9, 6.4)	6.6 (5.3, 7.8)	6.6 (5.3, 7.8)
Difference (Faricimab minus Aflibercept) (95% CI)	0.7 (-1.1, 2.5) [a]		0.0 (-1.7, 1.8) [a]	

BCVA change from baseline averaged over Weeks 52/56/60 (ETDRS letter score)				
Adjusted mean change (95% CI)	5.4 (4.0, 6.8)	4.6 (3.3, 6.0)	6.6 (5.3, 7.9)	7.1 (5.8, 8.4)
Difference (Faricimab minus Aflibercept) (95% CI)	0.7 (-1.2, 2.7)		-0.6 (-2.4, 1.3)	
Secondary endpoints				
Proportion of patients gaining ≥15 letters in BCVA from baseline averaged over Week 40/44/48				
Proportion (%) [b]	20.0%	15.7%	20.2%	22.2%
Difference (Faricimab minus Aflibercept) [c] (95% CI)	4.3% (-1.6%, 10.1%)		-2.0% (-8.3%, 4.3%)	
Proportion of patients gaining ≥10 letters in BCVA from baseline averaged over Week 40/44/48				
Proportion (%) [b]	37.1%	31.7%	39.2%	35.8%
Difference (Faricimab minus Aflibercept) [c] (95% CI)	5.4% (-2.0%, 12.7%)		3.4% (-3.9%, 10.7%)	
Proportion of patients avoiding loss of ≥15 letters in BCVA from baseline averaged over Week 40/44/48				
Proportion (%) [b]	95.4%	94.1%	95.8%	97.3%
Difference (Faricimab minus Aflibercept) [c] (95% CI)	1.3% (-2.2%, 4.8%)		-1.5% (-4.4%, 1.3%)	
Proportion of patients avoiding loss of ≥10 letters in BCVA from baseline averaged over Week 40/44/48				
Proportion (%) [b]	91.6%	92.0%	93.8%	94.6%
Difference (Faricimab minus Aflibercept) [c] (95% CI)	-0.4% (-4.6%, 3.9%)		-0.9% (-4.5%, 2.8%)	
Proportion of patients with BCVA Snellen equivalent of 20/40 or better averaged over Week 40/44/48				
Proportion (%) [b]	56.4%	57.0%	55.2%	49.4%
Difference (Faricimab minus Aflibercept) [c] (95% CI)	-0.5% (-7.7%, 6.6%)		5.7% (-1.4%, 12.9%)	
Proportion of patients with BCVA Snellen equivalent of 20/200 or worse averaged over Week 40/44/48				
Proportion (%) [b]	6.4%	6.9%	7.9%	7.5%
Difference (Faricimab minus Aflibercept) [c] (95% CI)	-0.5% (-4.2%, 3.3%)		0.4% (-3.6%, 4.4%)	
Change from baseline in CST (μm) averaged over Weeks 40/44/48				
Adjusted mean change	-136.8	-129.4	-137.1	-130.8
Difference (Faricimab minus Aflibercept) (95% CI)	-7.4 (-15.7, 0.8)		-6.4 (-14.8, 2.1)	
Change from baseline in total area of CNV lesion (mm^2) through Week 48				
Baseline CNV lesion area, mean	4.7	4.5	4.7	4.3
Adjusted mean change through Week 48 (95% CI)	0.0 (-0.6, 0.5)	0.4 (-0.2, 1.0)	0.3 (-0.2, 0.9)	1.1 (0.5, 1.6)
Change from baseline in total area of leakage CNV lesion (mm^2) through Week 48				
Baseline CNV lesion area, mean	7.0	7.0	7.2	6.4
Adjusted mean change through Week 48 (95% CI)	-3.8 (-4.7, -2.9)	-3.0 (-3.9, -2.1)	-3.3 (-4.2, -2.5)	-2.1 (-2.9, -1.3)
Proportion of patients with absence of IRF through Week 48				
Proportion (%) [b]	82.1%	74.4%	84.1%	77.7%
Difference (Faricimab minus Aflibercept) [c] (95% CI)	7.7% (1.0%, 14.4%)		6.4% (-0.0%, 12.9%)	

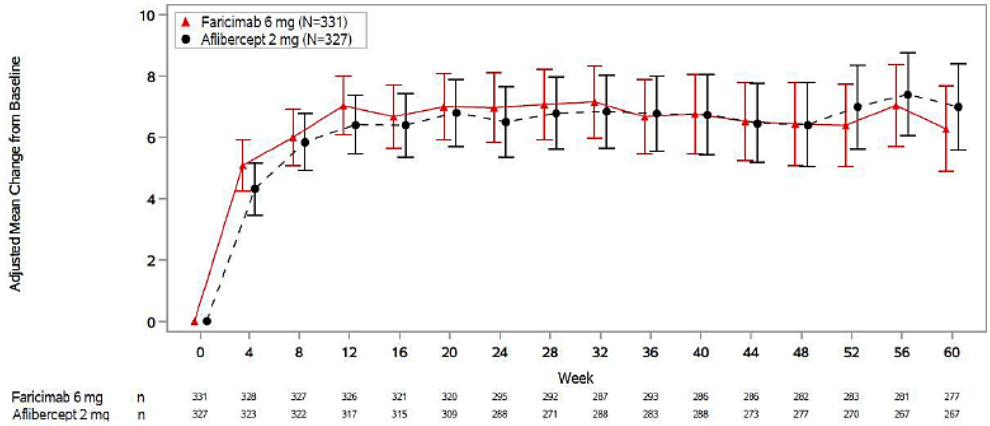
Proportion of patients with absence of SRF through Week 48				
Proportion (%) [b]	75.7%	65.8%	72.5%	62.1%
Difference (Faricimab minus Aflibercept) [c] (95% CI)	10.0% (2.6%, 17.3%)		10.4% (2.9%, 17.9%)	
Proportion of patients with absence of PED through Week 48				
Proportion (%) [b]	3.0%	7.7%	3.3%	6.5%
Difference (Faricimab minus Aflibercept) [c] (95% CI)	-4.6% (-8.3%, -1.0%)		-3.2% (-6.7%, 0.2%)	

The study eye results are presented. 95% CI is a rounding of 95.03% CI.
BCVA: best corrected visual acuity; CI: confidence interval; CNV: choroidal neovascularisation; CST: central subfield thickness; ETDRS: early treatment diabetic retinopathy study; IRF: intraretinal fluid; ITT: intent-to-treat; PED: pigment epithelial detachment; PP: per-protocol; SRF: subretinal fluid
[a] Non-inferiority was met as the lower bound of the two-sided 95.03% confidence interval for the difference in adjusted means between faricimab arm and aflibercept arm was greater than the pre-specified non-inferiority margin of -4 letters.
[b] Weighted estimated proportion is based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline BCVA, baseline low-luminance deficit and region.
[c] Weight estimated difference is based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline BCVA, baseline low-luminance deficit and region.

BCVA change from baseline in the study eye over time through Week 60 (Study TENAYA)



BCVA change from baseline in the study eye over time through Week 60 (Study LUCERNE)



Prespecified subgroup analyses in Studies TENAYA and LUCERNE demonstrated a consistent treatment effect for the primary endpoint across subgroups, including region (United States & Canada, rest of the world), baseline BCVA (73-55 letters, ≤54 letters), low-luminance deficit (<33 letters, ≥33 letters), age (<75 years, ≥75 years), gender (female, male), race (White), CNV lesion subtype (occult, classic), CNV lesion size (<1 mm^2, >3 mm^2), and total CNV lesion area (<1 mm^2, 1-3 mm^2, >3 mm^2).

Overall, the results from studies TENAYA and LUCERNE adequately supported the non-inferiority of faricimab 6 mg up to Q16W with aflibercept 2 mg Q8W for the treatment of nAMD.

Diabetic Macular Edema (DME)

Studies YOSEMITE and RHINE were Phase III, randomised, double-masked, ongoing, non-inferiority studies that compared faricimab 6 mg with aflibercept 2 mg in patients aged ≥18 years with DME and had BCVA of 73 to 25 letters on the ETDRS-like chart. The studies included patients who were naive to anti-VEGF therapy in the study eye and patients who had previously been treated with anti-VEGF therapy in the study eye, provided that the last treatment was at least 3 months prior to the Day 1 visit (the first study treatment. Patients were randomised in 1:1:1 ratio to one of 3 treatment arms. In Arm A (faricimab Q8W), IVT faricimab 6 mg was administered Q4W up to Week 20, followed by faricimab 6 mg Q8W to Week 96. In Arm B (faricimab Q16W adjustable dosing), IVT faricimab 6 mg was administered Q4W for at least 4 doses and until resolution of oedema based on the CST of the macula, followed by faricimab adjustable dosing interval to Week 96. The dosing interval could be modified by an interval extension of up to 4 weeks, interval maintenance, or reduction in 4- or 8-week interval decrement based on CST and BCVA evaluation at study drug dosing visits. In Arm C (aflibercept Q8W), IVT aflibercept 2 mg was administered Q4W up to Week 16, followed by aflibercept 2 mg Q8W to Week 96.

The primary efficacy endpoint was the change from baseline in BCVA averaged over Weeks 48, 52, and 56, as measured on the ETDRS letter score. The primary objective was to demonstrate non-inferiority between each faricimab dosing interval (Q8W and Q16W) and aflibercept in terms of the primary endpoint. Testing was performed independently for each faricimab dosing interval at an overall two-sided significance level of 0.0496 and in a hierarchical manner to control for the overall Type 1 error rate. Non-inferiority of faricimab was compared with aflibercept in the ITT population based on the pre-specified non-inferiority margin of 4 letters, then superiority of faricimab was compared with aflibercept in the treatment-naïve (TN) population, followed by superiority of faricimab compared with aflibercept in the ITT population.

The key secondary efficacy endpoint was the proportion of patients with ≥2-step diabetic retinopathy severity (DRS) improvement from baseline on the ETDRS DRS scale (DRSS) at Week 52. The key secondary hypothesis was tested independently for each of the faricimab dosing interval arms against aflibercept at an overall two-sided significance level of 0.0248 using a fixed sequence testing procedure to control for the overall Type I error rate. Testing was performed hierarchically: non-inferiority of faricimab was compared with aflibercept in the ITT population based on the pre-specified non-inferiority margin of 10%, then superiority of faricimab was compared with aflibercept in the TN population, followed by superiority of faricimab compared with aflibercept in the ITT population. Other secondary endpoints were the change from baseline in BCVA over time, proportion of patients gaining ≥15, ≥10, ≥5 or ≥0 letters from baseline BCVA, proportion of patients with BCVA Snellen equivalent of 20/40 or better, proportion of patients with BCVA Snellen equivalent of 20/200 or worse, proportion of patients with ≥2-step, ≥3-step, or ≥4-step DRS improvement on the ETDRS DRSS, proportion of patients who develop new or high-risk proliferative diabetic retinopathy (PDR), change in CST from baseline, and proportion of patients with absence of DME, IRF, SRF.

In Study YOSEMITE , a total of 940 patients were randomised and analysed in the Full Analysis Set, comprising 315 patients in the faricimab Q8W arm, 313 patients in the faricimab Q16W adjustable dosing arm, and 312 patients in the aflibercept Q8W arm. The patient demographics

and baseline disease characteristics were well-balanced between the treatment arms. The mean age was 62.2 years (range: 24.0 to 85.0 years), and 403 patients (42.9%) were ≥65 years of age. The majority of patients were male (59.8%) and White (78.1%). The median time since DME diagnosis was 3.1 years. The mean BCVA and CST values in the study eye at baseline were comparable among faricimab Q8W arm, faricimab Q16W adjustable dosing arm and aflibercept arm (mean BCVA: 62.0 vs 61.9 vs 64.0 letters; mean CST: 492.3 µm vs 485.8 µm vs 484.5 µm). The majority of the patients were not previously treated with anti-VEGF therapy (77.1%) and had mild non-proliferative diabetic retinopathy (NPDR) (baseline DRSS level 3: 27.6%) or moderate NPDR (baseline DRSS level 4: 27.1%).

In Study RHINE, a total of 951 patients were randomised and analysed in the Full Analysis Set, comprising 317 patients in the faricimab Q8W arm, 319 patients in the faricimab Q16W adjustable dosing arm, and 315 patients in the aflibercept Q8W arm. The patient demographics and baseline disease characteristics were well-balanced between the treatment arms. The mean age was 62.2 years (range: 26.0 to 91.0 years), and 409 patients (43.0%) were ≥65 years of age. The majority of patients were male (60.9%) and White (79.1%). The median time since DME diagnosis was 6.6 years. The mean BCVA and CST values in the study eye at baseline were comparable among faricimab Q8W arm, faricimab Q16W adjustable dosing arm and aflibercept arm (mean BCVA: 61.9 vs 62.5 vs 62.1 letters; mean CST: 466.2 µm vs 471.3 µm vs 477.3 µm). The majority of the patients were not previously treated with anti-VEGF therapy (79.6%) and had mild NPDR (baseline DRSS level 3: 29.0%) or moderate NPDR (baseline DRSS level 4: 25.1%).

Both studies demonstrated non-inferiority of faricimab with aflibercept in the mean change from baseline in BCVA to Weeks 48/52/56. The lower bound of the 95% CI for the adjusted mean difference between faricimab Q8W and aflibercept in the ITT population fell within the pre-specified non-inferiority margin of -4 letters (YOSEMITE: -0.2 letters [95% CI: -2.0, 1.6]; RHINE: 0.7 letters [95% CI: -1.1, 2.5]). Similar results were reported for the comparison between faricimab Q16W adjustable dosing and aflibercept (YOSEMITE: 1.5 letters [95% CI: -0.1, 3.2]; RHINE: 0.5 letters [95% CI: -1.1, 2.1]). The primary analysis results in the PP population were consistent with the results in the ITT population. In the TN population, the mean change from baseline in BCVA at Week 48/52/56 was not statistically significantly different between the faricimab and aflibercept arm in both studies.

The difference in the adjusted mean BCVA change from baseline to Weeks 92/96/100 between the faricimab Q8W arm and the aflibercept arm (YOSEMITE: -0.7 letters [95% CI: -2.6, 1.2]; RHINE: 1.5 letters [95% CI: -0.5, 3.6]) and between the faricimab Q16W adjustable dosing arm and the aflibercept arm (YOSEMITE: -0.7 letters [95% CI: -2.5, 1.2]; RHINE : 0.7 letters [95% CI: -1.3, 2.7]) were consistent with the results seen over Weeks 48/52/56.

Non-inferiority between the faricimab arms and the aflibercept arm for the key secondary endpoint was demonstrated in Study YOSEMITE study but not in Study RHINE. In Study YOSEMITE, the lower bound of the 97.5% CI for the difference in the adjusted proportion of patients with ≥2-step DRS improvement at Week 52 was greater than the pre-specified non-inferiority margin of -10% for the faricimab Q8W arm (10.2%; 97.5% CI: 0.3%, 20.0%) and the faricimab Q16W adjustable dosing arm (6.1%; 97.5% CI: -3.6%, 15.8%) compared to the aflibercept arm. However, in Study RHINE, the lower bound of the 97.5% CI for the difference exceeded the non-inferiority margin of -10% for the faricimab Q8W arm (-2.6%; 97.5% CI: -12.6%%, 7.4%) and the faricimab Q16W adjustable dosing arm (-3.5%; 97.5% CI: -13.4%, 6.3%) compared to aflibercept arm.

The inconsistency in the key secondary endpoint results between the two studies at Week 52 might be attributed to the variability in the DRS endpoint over time(?), considering that the difference between studies was not seen at longer follow-up to Week 96. At this timepoint, the difference in the adjusted proportion of patients with ≥2-step DRS improvement between the faricimab Q8W arm and the aflibercept arm was 9.1% (97.5% CI: 0.0%, 18.2%) in Study YOSEMITE and 9.7% (97.5% CI: 0.4%, 19.1%) in Study RHINE. Likewise, the difference in the adjusted proportion of patients between faricimab Q16W adjustable dosing arm and aflibercept arm was 0.0% (97.5% CI: -8.9%, 8.9%) in Study YOSEMITE study and 0.3% (97.5% CI: -8.9%, 9.5%) in Study RHINE.

The secondary outcomes were generally comparable between treatment arms with slight variations between the two studies. A higher proportion of patients with BCVA gain ≥15 letters was seen with the faricimab Q16W adjustable dosing arm as compared to the aflibercept arm in Study YOSEMITE (35.5% vs 31.8%), whereas the proportion was lower in Study RHINE (28.5% vs 30.3%). Similarly, the proportion of patients with ≥2-step DRS improvement from baseline on the ETDRS DRSS at Week 52 was higher in the faricimab Q16W adjustable dosing arm as compared to the aflibercept arm in the Study YOSEMITE (42.1% vs 36.7%), while an opposite trend was observed in the Study RHINE (43.4% vs 47.5%).

Summary of Key Efficacy Results (Studies YOSEMITE and RHINE)

	Study YOSEMITE			Study RHINE		
	Faricimab Q8W (N = 315)	**Faricimab Q16W adjustable dosing (N = 313)**	**Aflibercept Q8W (N = 312)**	**Faricimab Q8W (N = 317)**	**Faricimab Q16W adjustable dosing (N = 319)**	**Aflibercept Q8W (N = 315)**
Primary endpoint - BCVA change from baseline averaged over Weeks 48/52/56 (ETDRS letter score)						
ITT population						
Adjusted mean change (97.5% CI)	10.7 (9.4, 12.0)	11.6 (10.3, 12.9)	10.9 (9.6, 12.2)	11.8 (10.6, 13.0)	10.8 (9.6, 11.9)	10.3 (9.1, 11.4)
Difference vs aflibercept (97.5% CI)	-0.2 (-2.0, 1.6) [a]	0.7 (-1.1, 2.5) [a]	-	1.5 (-0.1, 3.2) [a]	0.5 (-1.1, 2.1) [a]	-
PP population						
Adjusted mean change (97.5% CI)	10.8 (9.4, 12.1)	11.8 (10.5, 13.2)	11.2 (9.9, 12.5)	11.9 (10.6, 13.2)	10.7 (9.5, 12.0)	10.4 (9.1, 11.6)
Difference vs aflibercept (97.5% CI)	-0.4 (-2.3, 1.5) [a]	0.7 (-1.2, 2.5) [a]	-	1.5 (-0.3, 3.3)	0.3 (-1.4, 2.1)	-
TN population						
Adjusted mean change (97.5% CI)	10.6 (9.1, 12.1)	11.4 (9.9, 12.8)	11.3 (9.8, 12.8)	11.7 (10.4, 13.0)	11.2 (9.9, 12.4)	10.5 (9.2, 11.9)
Difference vs aflibercept (97.5% CI)	-0.7 (-2.8, 1.4)	0.0 (-2.1, 2.2)	-	1.1 (-0.7, 3.0)	0.6 (-1.2, 2.4)	-
BCVA change from baseline averaged over Weeks 92/96/100 (ETDRS letter score)						
ITT population						
Adjusted mean change (97.5% CI)	10.7 (9.4, 12.1)	10.7 (9.4, 12.1)	11.4 (10.0, 12.7)	10.9 (9.5, 12.3)	10.1 (8.7, 11.5)	9.4 (7.9, 10.8)
Difference vs aflibercept (97.5% CI)	-0.7 (-2.6, 1.2)	-0.7 (-2.5, 1.2)	-	1.5 (-0.5, 3.6)	0.7 (-1.3, 2.7)	-
Key secondary endpoint - Proportion of patients with a ≥2-step improvement from baseline on the ETDRS DRS scale at Week 52						
ITT population						
Proportion (%)	45.6%	42.1%	36.7%	44.2%	43.4%	47.5%

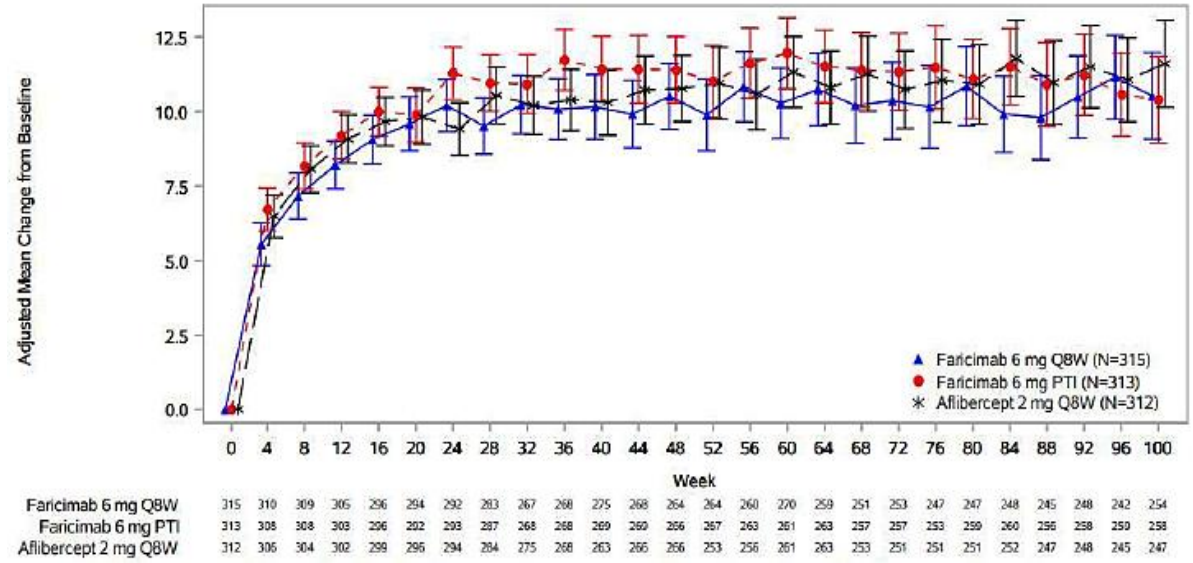
Difference vs aflibercept [b] (97.5% CI)	10.2% (0.3, 20.0) [c]	6.1% (-3.6, 15.8) [c]	-	-2.6% (-12.6, 7.4) [d]	-3.5% (-13.4, 6.3) [d]	-
PP population						
Proportion (%)	46.0%	42.9%	38.4%	45.6%	45.5%	47.3%
Difference vs aflibercept [b] (97.5% CI)	9.1% (-1.2, 19.3)	4.9% (-5.2, 15.0)	-	-1.0% (-11.4, 9.4)	-1.6% (-11.8, 8.6)	-
TN population						
Proportion (%)	49.7%	47.6%	43.0%	46.9%	45.5%	52.7%
Difference vs aflibercept [b] (97.5% CI)	7.2% (-4.6, 18.9)	4.8% (-6.7, 16.3)	-	-5.4% (-16.9, 6.1)	-6.9% (-18.3, 4.4)	
Secondary endpoint (ITT population)						
Proportion of patients gaining ≥15 letters in BCVA from baseline averaged over Week 48/52/56						
Proportion (%)	29.2%	35.5%	31.8%	33.8%	28.5%	30.3%
Difference vs aflibercept [b] (95% CI)	-2.6% (-10.0, 4.9)	3.5% (-4.0, 11.1)	-	3.5% (-4.0, 11.1)	-2.0% (-9.1, 5.2)	-
Proportion of patients with BCVA Snellen equivalent of 20/40 or better averaged over Week 48/52/56						
Proportion (%)	72.0%	77.2%	74.6%	73.1%	71.7%	68.8%
Difference vs aflibercept [b] (95% CI)	-3.2% (-10.2, 3.8)	2.4% (-4.3, 9.2)	-	4.7% (-2.4, 11.8)	2.8% (-4.1, 9.8)	-
Proportion of patients with BCVA Snellen equivalent of 20/200 or worse averaged over Week 48/52/56						
Proportion (%)	2.2%	1.8%	1.8%	0.7%	0.0%	0.7%
Difference vs aflibercept [b] (95% CI)	0.6% (-1.8, 2.9)	0.0% (-2.2, 2.3)	-	0.1% (-1.4, 1.5)	-0.7% (-1.6, 0.2)	-
Proportion of patients with a ≥3-step improvement from baseline on the ETDRS DRS scale at Week 52						
Proportion (%)	16.5%	15.3%	15.3%	16.5%	18.7%	19.7%
Difference vs aflibercept [b] (95% CI)	1.2% (-5.5, 7.8)	0.0% (-6.5, 6.5)	-	-3.3% (-10.3, 3.7)	-1.0% (-8.0, 6.0)	-
Proportion of patients with a ≥2-step worsening from baseline on the ETDRS DRS scale at Week 52						
Proportion (%)	0.8%	0.4%	1.3%	0.9%	0.4%	0.4%
Difference vs aflibercept [b] (95% CI)	-0.5% (-2.3, 1.4)	-0.9% (-2.6, 0.8)	-	0.4% (-1.0, 1.9)	0 0	-
Proportion of patients who developed new PDR at Week 52						
Proportion (%)	0.9%	0.9%	0	0.9%	0.9%	0.5%
Difference vs aflibercept [b] (95% CI)	0.4% (-1.1, 2.0)	0.4% (-1.1, 2.0)	-	0.5% (-1.1, 2.0)	0.5% (-1.1, 2.0)	-
Change from baseline in CST (µm) averaged over Weeks 48/52/56						
Adjusted mean change	-206.6	-196.5	-170.3	-195.8	-187.6	-170.1
Difference vs aflibercept (95% CI)	-36.2 (-47, -24)	-26.2 (-37, -14)	-	-25.7 (-37.4, -14.0)	-17.6 (-29.2, -6.0)	-
Proportion of patients with absence of DME [e]						
Proportion (%)	81.3%	77.9%	65.1%	85.4%	81.6%	73.1%
Difference vs aflibercept [b] (95% CI)	16.0% (8.9, 23.1)	12.7% (5.4, 20.0)	-	12.3% (5.7, 18.9)	8.2% (1.5, 14.9)	-

The study eye results are presented. 97.5% CI is a rounding of 97.52% CI.
BCVA: best corrected visual acuity; CI: confidence interval; CST: central subfield thickness; DRS: diabetic retinopathy severity; ETDRS: Early Treatment Diabetic Retinopathy Study; IRF: intraretinal fluid; ITT: intent-to-treat; n: number of patients; PP: per-protocol; Q16W adjustable dosing: treatment interval adjustable from Q4W up to Q16W; SRF: subretinal fluid; TN: treatment-naïve

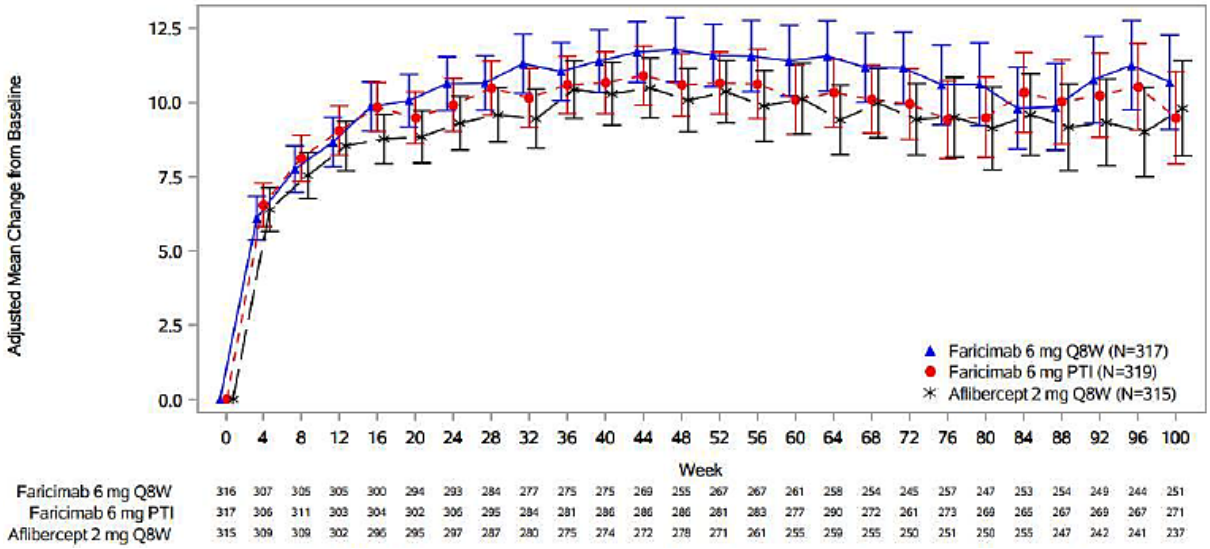
[a] Non-inferiority was met as the lower bound of the two-sided 97.5% confidence interval for the difference in adjusted means between faricimab arm and aflibercept arm was greater than the pre-specified non-inferiority margin of -4 letters.

[b] Weighted estimated proportion is based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline BCVA, region, and prior anti-VEGF therapy.
[c] Non-inferiority was met as the lower bound of the two-sided 97.5% confidence interval for the difference in proportion between faricimab arm and aflibercept arm was greater than the pre-specified non-inferiority margin of -10%.
[d] Non-inferiority was not met as the lower bound of the two-sided 97.5% confidence interval for the difference in proportion between faricimab arm and aflibercept arm was less than the pre-specified non-inferiority margin of -10%.
[e] Defined as CST <325 µm using Spectralis spectral domain optical coherence tomography (SD-OCT)

BCVA change from baseline in the study eye over time through Week 100 (Study YOSEMITE)



BCVA change from baseline in the study eye over time through Week 100 (Study RHINE)



Among patients who were on faricimab Q12W or Q16W at Week 52, the proportion of patients who was maintained on this interval without a decrease in interval below Q12W through Week 96 was 75.0% in Study YOSEMITE and 83.5% in Study RHINE. The proportion of patients without an interval decrease below Q16W was 69.9% in Study YOSEMITE and 81.8% in Study RHINE. At Week 96, the proportion of patients in the faricimab Q16W adjustable dosing arm who achieved a Q16W or Q12W dosing interval was 60% or 18.1% in Study YOSEMITE, and 64.5% and 13.6% in Study RHINE. Through Week 96, 4% of patients in Study YOSEMITE and 6% of patients in Study RHINE had their dosing intervals extended? (should it be “shortened”?) to Q8W interval.

Prespecified subgroup analyses in both studies demonstrated a consistent treatment effect for the primary endpoint across subgroups, including region (United States & Canada, Asia, rest of the world), baseline BCVA (≥64 letters, ≤63 letters), age (<65 years, ≥65 years), gender (male, female), race (White, Asian, Other), prior IVT anti-VEGF (yes, no), baseline DRSS (<47, 47-53, >53), and baseline HbA1c (≤8%, >8%).

Overall, the results from studies YOSEMITE and RHINE adequately supported the non-inferiority of faricimab 6 mg Q16W adjustable dosing regimen when compared with aflibercept 2 mg Q8W for the treatment of visual impairment due to DME.

D ASSESSMENT OF CLINICAL SAFETY

Neovascular Age-related Macular Degeneration (nAMD)

The safety data supporting the use of faricimab for patients with nAMD were mainly derived from studies TENAYA and LUCERNE, comprising a total of 1,326 patients. The median duration of exposure was the same between treatment arms in the two studies (60.1 weeks). The mean number of study drug administrations through Week 60 was lower in the faricimab arm compared to the aflibercept arm in the pooled data for TENAYA and LUCERNE studies (7.4 injections in faricimab arm and 8.5 injections in aflibercept arm).

Overview of Safety Profile through Week 60

Number (%) of patients with:	Pooled TENAYA and LUCERNE studies	
	Faricimab 6 mg (N = 664)	Aflibercept 2 mg (N = 662)
Ocular events in study eye		
AEs	278 (41.9%)	266 (40.2%)
Treatment-related AEs	19 (2.9%)	18 (2.7%)
SAEs	14 (2.1%)	17 (2.6%)
Treatment-related SAEs	8 (1.2%)	2 (0.3%)
AEs leading to treatment discontinuation	9 (1.4%)	5 (0.8%)
AEs of special interest	11 (1.7%)	16 (2.4%)
Drop in VA score ≥30 letters	8 (1.2%)	12 (1.8%)
Associated with severe IOI	1 (0.2%)	2 (0.3%)
Intervention required to prevent permanent vision loss	2 (0.3%)	2 (0.3%)
Non-ocular events		
AEs	388 (58.4%)	398 (60.1%)
SAEs	76 (11.4%)	94 (14.2%)
AEs leading to treatment discontinuation	7 (1.1%)	4 (0.6%)
Adjudicated APTC events	13 (2.0%)	10 (1.5%)
Non-fatal MI	3 (0.5%)	2 (0.3%)
Non-fatal Stroke	3 (0.5%)	3 (0.5%)
Death	7 (1.1%)	5 (0.8%)

AE: adverse event; APTC: anti-platelet Trialists' Collaboration; IOI: intraocular inflammation; MI: myocardial infarction; SAE: serious adverse event; VA: visual acuity

The percentage of patients with ocular adverse events (AEs) in the study eye was slightly higher in the faricimab arm compared to the aflibercept arm (41.9% vs 40.2%). AEs that were reported more frequently in the faricimab arm than the aflibercept arm included vitreous detachment (3.3% vs 3.0%), cataract (3.0% vs 2.1%), intraocular pressure increased (2.6% vs 2.3%), vitreous floaters (3.0% vs 1.7%), retinal pigment epithelial tear (2.9% vs 1.4%), blepharitis (1.4% vs 1.2%), posterior capsule opacification 1.5% vs 1.1%), eye irritation (1.4% vs 0.6%), uveitis (0.5% vs 0.3%), and ocular discomfort (1.2% vs 0.6%). Most AEs were mild or moderate in severity. AEs related to study drug were reported at a slightly higher incidence in the faricimab arm than the aflibercept arm (2.9% vs 2.7%) and driven by the higher number of patients with treatment-related retinal pigment epithelial tear (1.2% vs 0.3%).

The incidence of ocular serious adverse events (SAEs) in the study eye was low and comparable between the faricimab arm and the aflibercept arm (1.7% vs 2.0%). Ocular SAEs that were reported more frequently in the faricimab arm than the aflibercept arm included retinal pigment epithelial tear (0.6% vs 0%), uveitis (0.3% vs 0.2%), viral uveitis (0.3% vs 0%), vitritis (0.3% vs 0%), cataract (0.2% vs 0%), chorioretinitis (0.2% vs 0%), and intraocular pressure increased (0.2% vs 0%). Ocular SAEs related to the study treatment were retinal pigment epithelial tear (0.6%), uveitis (0.3%) and vitritis (0.3%) in the faricimab arm, and uveitis (0.3%) in the aflibercept arm.

Ocular AEs leading to permanent discontinuation of the study drug were low and reported at a higher incidence rate in the faricimab arm than the aflibercept arm (1.4% vs 0.8%). Those reported more frequently in the faricimab arm than the aflibercept arm were uveitis, iridocyclitis, nAMD, retinal pigment epithelial tear, vitreous detachment and vitritis (0.2% [1 patient] vs 0% each in all cases).

AEs of special interest for faricimab were retinal pigment epithelial tear and intraocular inflammation (IOI). Four patients (0.6%) in the faricimab arm experienced serious retinal pigment epithelial tear, two patients of whom were associated with vision loss of ≥15 to <30 letters and 1 patient with vision loss of ≥30 letters; these events did not resolve by Week 60. The IOI event rates were higher in faricimab arm than aflibercept arm (2.3% vs 1.5%). Three patients in the faricimab arm experienced IOI events in the study eye that were associated with vision loss of ≥15 letters, two of whom were related to study treatment, and all of these events were resolving or had resolved by Week 60. There were no IOI events associated with retinal vasculitis or occlusive disease in any treatment arms during the study follow-up period. These safety concerns have been described in the package insert and will be monitored as part of routine pharmacovigilance.

Overall, the safety profile of faricimab 6 mg up to Q16W interval for the treatment of nAMD was generally similar to aflibercept 2 mg Q8W, with retinal epithelial tear and IOI being the predominant adverse events. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

<u>Diabetic Macular Edema (DME)</u>

The safety data supporting the use of faricimab for patients with DME were mainly derived from studies YOSEMITE and RHINE, comprising a total of 1,887 patients. The median duration of exposure was the same among the treatment arms in both studies (96.1 weeks). The median number of study drug administrations was lower in the faricimab Q16W adjustable dosing arm (11.0 injections) compared to the faricimab Q8W arm (15.0 injections) and aflibercept arm (14.0 injections).

Overview of Safety Profile through Week 100

Number (%) of patients with:	Pooled TENAYA and LUCERNE studies		
	Faricimab 6 mg Q8W (N = 630)	Faricimab 6 mg Q16W adjustable dosing (N = 632)	Aflibercept 2 mg Q8W (N = 625)
Ocular events in study eye			
AEs	313 (49.7%)	311 (49.2%)	284 (45.4%)
Treatment-related AEs	21 (3.3%)	41 (3.2%)	21 (3.4%)
SAEs	26 (4.1%)	34 (5.4%)	20 (3.2%)
Treatment-related SAEs	7 (1.1%)	7 (0.6%)	0
AEs leading to treatment discontinuation	12 (1.9%)	17 (1.3%)	2 (0.3%)
AEs of special interest	25 (4.0%)	33 (5.2%)	20 (3.2%)
Drop in VA score ≥30 letters	18 (2.9%)	23 (3.6%)	16 (2.6%)
Associated with severe IOI	3 (0.5%)	5 (0.8%)	1 (0.2%)
Intervention required to prevent permanent vision loss	6 (1.0%)	8 (1.3%)	4 (0.6%)
Non-ocular events			
AEs	460 (73.0%)	469 (74.2%)	473 (75.7%)
SAEs	175 (27.8%)	161 (25.5%)	173 (27.7%)
AEs leading to treatment discontinuation	10 (1.6%)	6 (0.9%)	8 (1.3%)
Adjudicated APTC events	34 (5.4%)	30 (4.7%)	32 (5.1%)
Non-fatal MI	7 (1.1%)	5 (0.8%)	7 (1.1%)
Non-fatal Stroke	11 (1.7%)	10 (1.6%)	11 (1.8%)
Death	16 (2.5%)	15 (2.4%)	14 (2.2%)

The percentage of patients with ocular AEs in the study eye was higher in faricimab Q16W adjustable dosing arm compared to aflibercept arm (49.2% vs 45.4%). AEs that were reported more frequently in the faricimab Q16W adjustable dosing arm as compared to the aflibercept arm included cataract (13.6% vs 12.2%), conjunctival haemorrhage (7.0% vs 6.6%), vitreous detachment (4.4% vs 4.2%), dry eye (4.3% vs 2.7%), intraocular pressure increased (3.3% vs 2.6%), diabetic retinal oedema (2.7% vs 2.2%), conjunctivitis (2.1% vs 1.8%), cataract subcapsular (1.6% vs 1.3%), blepharitis (1.4% vs 0.6%), diabetic retinopathy (2.1% vs 1.1%), cataract nuclear (1.4% vs 1.1%), lacrimation increased (1.7% vs 0.6%), ocular hypertension (1.3% vs 0.3%) and visual impairment (1.3% vs 0.5%). The majority of the AEs were mild or moderate in severity. Ocular AEs related to study drug were reported at similar incidence in faricimab Q16W adjustable dosing arm (3.2%) and aflibercept arm (3.4%). The most common treatment-related ocular AEs in the study eye in faricimab Q16W adjustable dosing arm (≥0.5% incidence) were intraocular pressure increased (0.9%), cataract (0.5%) and uveitis (0.5%).

The incidence of ocular SAEs in the study eye was higher in the faricimab Q16W adjustable dosing arm compared to the aflibercept arm (5.4% vs 3.2%). Those reported at a numerically higher incidence rate in the faricimab Q16W adjustable dosing arm than the aflibercept arm included cataract (1.4% vs 1.3%), diabetic retinal oedema (0.5% vs 0.2%), endophthalmitis (0.6% vs 0.2%), retinal tear (0.5% vs 0%), retinal vein occlusion (0.5% vs 0%), uveitis (0.5% vs 0%), angle closure glaucoma (0.2% vs 0%), visual impairment (0.3% vs 0%), and chorioretinitis, diabetic eye disease, keratouveitis, ocular hypertension, ocular ischaemic syndrome, open angle glaucoma, posterior capsule opacification, posterior capsule rupture,

and uveitic glaucoma (0.2% vs 0% each). Ocular SAEs related to study treatment in the faricimab Q16W adjustable dosing arm were uveitis (0.5%), and cataract, chorioretinitis, diabetic eye disease, keratouveitis, and open angle glaucoma (0.2% each).

Ocular AEs leading to permanent discontinuation of the study drug were reported at a higher frequency in the faricimab Q16W adjustable dosing arm than the aflibercept arm (1.9% vs 0.3%). Those that were reported more frequently in the faricimab Q16W adjustable dosing arm than the aflibercept arm were endophthalmitis (0.5% vs 0.2%), uveitis (0.5% vs 0%), and angle closure glaucoma, corneal infiltrates, diabetic eye disease, open angle glaucoma, and retinal vein occlusion (0.2% each).

AEs of special interest for faricimab were intraocular inflammation (IOI) and intraocular pressure increased. IOI events were reported in 1.7% of patients in faricimab Q16W adjustable dosing arm and 1.1% of patients in aflibercept arm, and majority of the events were mild or moderate in severity. Two patients in the faricimab Q16W adjustable dosing arm experienced IOI events (uveitis and keratic precipitates) in the study eye that were associated with vision loss of ≥30 letters and were related to study treatment. There were no IOI events associated with retinal vasculitis or occlusive disease in any treatment arms during the study follow-up period. Intraocular pressure increased was reported in 21 patients (3.3%) in the faricimab Q16W adjustable dosing arm and 16 patients (2.6%) in the aflibercept arm, of which, 8 patients (1.3%) and 2 patients (0.3%) respectively developed ocular hypertension. These safety concerns have been described in the package insert and required to be monitored as part of routine pharmacovigilance.

Overall, the safety profile of faricimab 6 mg Q16W adjustable dosing for the treatment of DME was generally similar to aflibercept 2 mg Q8W, with IOI and increased intraocular pressure being the predominant adverse events. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Neovascular Age-related Macular Degeneration (nAMD)

nAMD is a chronic and progressive disease of the macula that could lead to irreversible vision loss. Anti-VEGF intravitreal injections are used in the management of nAMD for the maintenance of visual acuity.

Studies TENAYA and LUCERNE demonstrated non-inferiority of faricimab 6 mg up to the Q16W dosing interval when compared with aflibercept 2 mg Q8W in the mean change from baseline in BCVA over Weeks 40, 44, and 48. The observed visual acuity improvements were maintained through Week 60. A comparable proportion of patients treated with faricimab or aflibercept gained ≥15 letters in BCVA and achieved BCVA Snellen equivalent 20/40 or better from baseline to Weeks 40, 44, and 48. The reduction in CST and the proportion of patients with absence of IRF, SRF or PED through Week 48 were similar between the faricimab and aflibercept arms in both studies.

The safety profile of faricimab 6 mg up to Q16W dosing was generally similar to that of aflibercept 2 mg Q8W. Adverse events of interest for faricimab are retinal epithelial tear and intraocular inflammation which have been adequately addressed in the local package insert via the provision of relevant warnings and precautions.

Overall, the benefit-risk profile of faricimab for treatment of nAMD was considered positive.

Diabetic Macular Edema (DME)

DME is a progressing complication of diabetic retinopathy that could lead to central vision loss. Alongside dietary and pharmacological management of the underlying diabetes mellitus disease, DME is managed with anti-VEGF intravitreal injections to maintain visual acuity.

Studies YOSEMITE and RHINE demonstrated non-inferiority of faricimab 6 mg up to Q16W adjustable dosing interval to aflibercept 2 mg Q8W with respect to mean change from baseline in BCVA over Weeks 48, 52, and 56. The observed visual acuity improvements were maintained through Week 100. The proportion of patients with ≥2-step DRS improvement from baseline through Week 52 for faricimab Q16W adjustable dosing arm was shown to be non-inferior to aflibercept in Study YOSEMITE but not in Study RHINE. Nonetheless, the proportion was numerically comparable between the treatment arms in Study RHINE. A comparable proportion of patients treated with faricimab or aflibercept gained ≥15 letters in BCVA and achieved BCVA Snellen equivalent 20/40 or better from baseline to Weeks 48, 52, and 56. The reduction in CST, proportion of patients who developed new PDR and those with absence of DME through Week 52 were similar between the faricimab Q16W adjustable dosing arm and the aflibercept arm in both studies.

The safety profile of faricimab 6 mg up to Q16W adjustable dosing was generally similar to that of aflibercept 2 mg Q8W. Adverse events of interest for faricimab are intraocular inflammation and increased intraocular pressure which have been adequately addressed in the local package insert via the provision of relevant warnings and precautions.

Overall, the benefit-risk profile of faricimab for treatment of DME was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of faricimab was deemed favourable for the treatment of neovascular age-related macular degeneration and visual impairment due to diabetic macular edema. Approval of the product registration was granted on 16 June 2022.

APPROVED PACKAGE INSERT AT REGISTRATION

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

INJ-VAB-2022 06

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 in a single-dose glass vial, containing 28.8 mg faricimab in 0.24 mL solution. This provides a usable amount to deliver a single dose of 0.05 mL solution containing 6 mg of faricimab.

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).

2.2 DOSAGE AND 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 solution) administered by intravitreal injection every 4 weeks for the first 4 doses, followed by anatomic and visual acuity evaluations at Week 20 and Week 24 to inform dosing Vabysmo at intervals of 8, 12, or 16 weeks through week 60. The use of Vabysmo beyond Week 60 has not been assessed (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 4 doses or 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 up to every 16 weeks, in up to 4-week increments. 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.

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 and retinal tear. Proper aseptic injection techniques must always be used when administering Vabysmo. Patients should be instructed to report any symptoms, such as pain, loss of vision, photophobia, blurred vision, floaters, or redness, suggestive of endophthalmitis or any of the above-mentioned events without delay, to permit prompt and appropriate management.

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.

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 and DME patients with active systemic infections. There is also no experience of treatment with Vabysmo in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

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

Treatment of nAMD
The most frequently reported serious adverse reactions in patients treated with Vabysmo were retinal pigment epithelial (RPE) tear (0.6%), vitritis (0.3%), uveitis (0.3%), visual acuity reduced (0.2%) and cataract (0.2%).

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

The adverse reactions (regardless of causality) leading to permanent discontinuation of Vabysmo were 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.

Tabulated summary of adverse drug reactions from clinical trials
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 60 (see section 3.1.2 Clinical Efficacy Studies).

Table 1 Adverse Reactions (≥ 1%) in the TENAYA and LUCERNE nAMD Studies through Week 60

Adverse Reactions SOC Preferred Term MedDRA version 23.1	Vabysmo n = 664	Aflibercept n = 662
Eye disorders		
Conjunctival haemorrhage	8%	8%
Cataract	5%	3%
Vitreous detachment	4%	3%
Vitreous floaters	3%	2%
Retinal pigment epithelial tear	3%	2%
Intraocular pressure increased	3%	3%
Eye pain	3%	3%

Intraocular inflammation[a]	2%	< 1%
Eye irritation	1%	< 1%
Corneal abrasion	1%	1%
Ocular discomfort	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

Description of selected adverse drug reactions from clinical trials
Arterial Thromboembolic Events (ATEs)
The incidence of reported ATEs in the nAMD studies during Week 60 was 2% (13 out of 664) in patients treated with Vabysmo compared with 2% (10 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).

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 for up to 48 weeks (nAMD) and 100 weeks (DME), treatment-emergent anti-faricimab antibodies (ADA) were detected in approximately 10.4% of nAMD patients and 9.6% of DME patients. The clinical significance of anti-faricimab antibodies on safety is unclear at this time. Among the patients with anti-faricimab antibodies, a higher incidence of intraocular inflammation adverse reactions were observed in 5 out of 75 (nAMD) and 15 out of 128 (DME) ADA-positive patients and in 7 out of 582 (nAMD) and 5 out of 1124 (DME) ADA-negative patients however, the overall incidence of anti-faricimab antibody positivity and intraocular inflammation in the entire trial population is approximately 1%. 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 (1.4%). 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
Not applicable

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 and DME 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 four clinical trials (TENAYA, LUCERNE, RHINE, and YOSEMITE).

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).

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.

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, and 1,326 patients received at least one dose (664 with Vabysmo). Patient ages ranged from 50 to 99 with a mean of 75.9 years.

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

After the first four monthly doses (weeks 0, 4, 8, and 12) patients randomized to the Vabysmo arm received Q16W, every 12 weeks (Q12W) or Q8W dosing based on an assessment of disease activity at weeks 20 and 24, using objective pre-specified 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.

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. The results are summarized in Table 3 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%

Table 3 Baseline Characteristics[a] and Efficacy outcomes at the primary endpoint visits[b] in TENAYA and LUCERNE

Efficacy Outcomes	TENAYA		LUCERNE	
	Vabysmo up to Q16W N = 334	Aflibercept Q8W N = 337	Vabysmo up to Q16W N = 331	Aflibercept Q8W N = 327
Median number of injections received [Q1, Q3]	6.0 [6, 7]	8.0 [7, 8]	6.0 [6, 7]	8.0 [7, 8]
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]	6.6 [5.3, 7.8]	6.6 [5.3, 7.8]
Difference in LS mean [95% CI]	0.7 [-1.1, 2.5][c]		0.0 [-1.7, 1.8][c]	
Proportion of patients with ≥ 15 letter gain from baseline [CMH weighted proportion, 95% CI]	20.0% [15.6%, 24.4%]	15.7% [11.9%, 19.6%]	20.2% [15.9%, 24.6%]	22.2% [17.7%, 26.8%]
Difference in CMH weighted % [95% CI]	4.3% [-1.6%, 10.1%]		-2.0% [-8.3%, 4.3%]	
Proportion of patients avoiding ≥ 15 letter loss from baseline [CMH weighted proportion, 95% CI]	95.4% [93.0%, 97.7%]	94.1% [91.5%, 96.7 %]	95.8% [93.6%, 98.0%]	97.3% [95.5%, 99.1%]
Difference in CMH weighted % [95% CI]	1.3% [-2.2%, 4.8%]		-1.5% [-4.4%, 1.3%]	

[a]Baseline ocular characteristics were well balanced between treatment arms and across studies
[b]Average of weeks 40, 44 and 48
[c]Met the pre-specified non-inferiority margin of 4 letters for the primary endpoint in both studies
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 48 in TENAYA

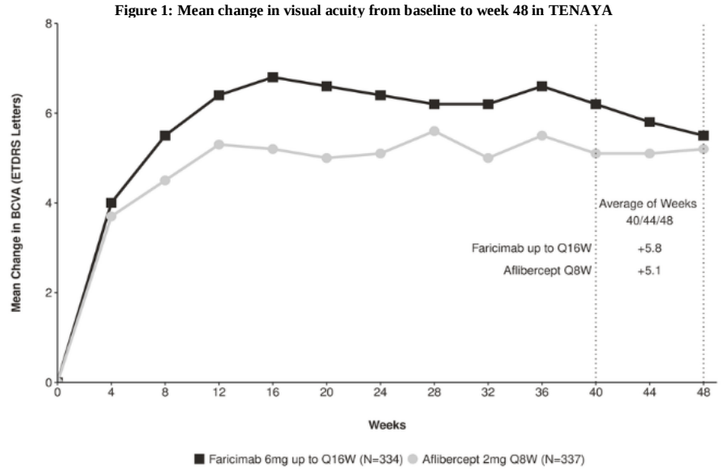
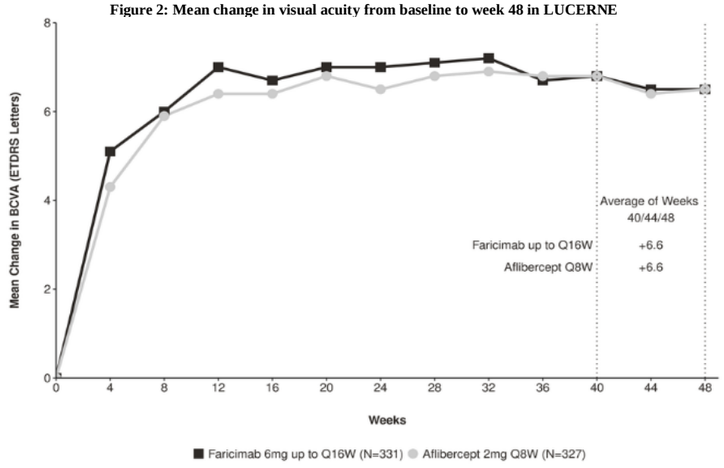


Figure 2: Mean change in visual acuity from baseline to week 48 in LUCERNE



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 4, 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 4 and Figures 3 and 4 below.

Table 4 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 = 262	Vabysmo up to Q16W adjustable dosing N = 270	Aflibercept Q8W N = 259	Vabysmo Q8W N = 317	Vabysmo up to Q16W adjustable dosing N = 319	Aflibercept Q8W N = 315	Vabysmo Q8W N = 259	Vabysmo up to Q16W adjustable dosing N = 282	Aflibercept Q8W N = 254
Mean 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	7.6	5.1	4.2				6.3	6.0	5.4			
Type 2	92.4	95.5	95.8				93.7	94.0	94.6			
Diabetic Retinopathy Status (%)												
DRS levels 10-20 (DR Absent/ Questionable/ Microaneurysms only)	1.9	2.9	4.5				1.5	4.4	2.2			
DRS levels 35-43 (mild and moderate NPDR)	53.4	56.9	53.8				56.2	51.4	54.9			
DRS levels 47-53 (moderately severe and severe NPDR)	35.9	31.6	33.0				34.4	31.0	33.3			
DRS level 61-85 (PDR)	7.0	6.7	5.7				6.3	11.6	6.4			
Cannot grade	1.3	1.6	2.2				0.6	1.6	1.6			
Missing	0.6	0.3	0.6				0.9	0.0	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

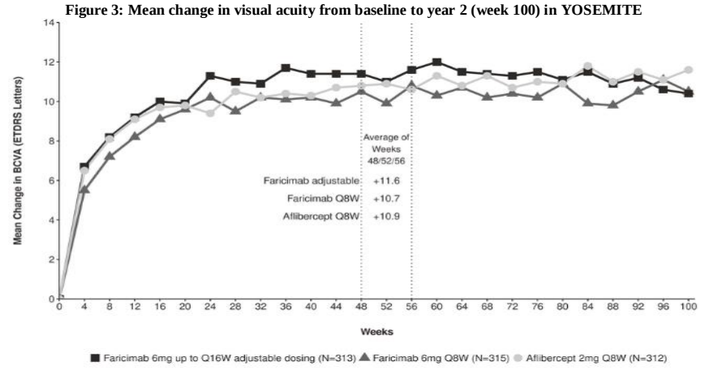
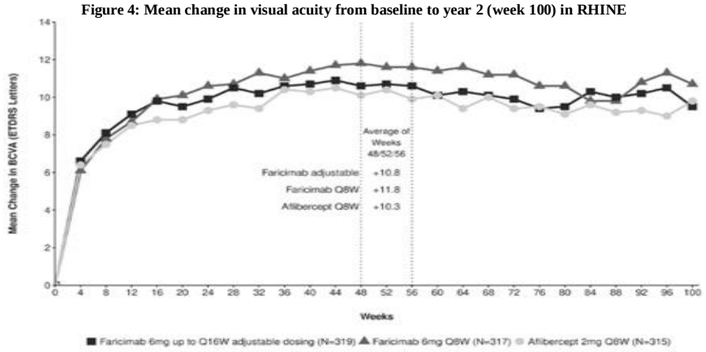


Figure 4: Mean change in visual acuity from baseline to year 2 (week 100) in RHINE



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 5 below.

Table 5 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	VabysmoQ8W n = 231	Vabysmo up to Q16W adjustable dosing n = 251	Aflibercept Q8W n = 238	VabysmoQ8W 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% (1.6%, 18.7%)	6.1% (-2.4%, 14.6%)		9.1% (0.0%, 18.2%)	0.0% (-8.9%, 8.9%)		-2.6% (-11.3%, 6.2%)	-3.5% (-12.1%, 5.1%)		9.7% (0.4%, 19.1%)	0.3% (-8.9%, 9.5%)	
Proportion of patients with ≥ 3-step ETDRS-DRSS improveme	16.8%	15.5%	14.7%	22.4%	14.6%	20.9%	16.7%	18.9%	19.4%	25.1%	19.3%	21.8%

nt from baseline (CMH weighted proportion)												
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.

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.

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.

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 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 four Phase III clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with Vabysmo were ≥ 65 years of age. Population pharmacokinetic analysis has shown an effect of age on ocular pharmacokinetics of faricimab. The effect was considered not clinically meaningful.

Renal impairment
No formal pharmacokinetic study has been conducted with Vabysmo in patients with renal impairment. Pharmacokinetic analysis of patients in all clinical studies of which 64% had renal impairment (mild 38%, moderate 24%, and severe 2%), revealed no differences with respect to systemic pharmacokinetics of faricimab after intravitreal administration of Vabysmo.

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 in the original carton to protect from light.

Prior to use, the unopened vial of Vabysmo may be kept at room temperature, 20°C to 25°C (68°F to 77°F), for up to 24 hours.

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

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

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. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

The contents of the vial and transfer filter needle are sterile and for single use only. Do not use if the packaging, vial and/or transfer filter needle are damaged or expired.

Use aseptic technique for preparation of the intravitreal injection.

Instructions for administration
See section 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 June 2022

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

Instructions For Use - 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.

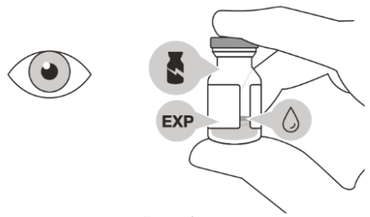


Figure A

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.

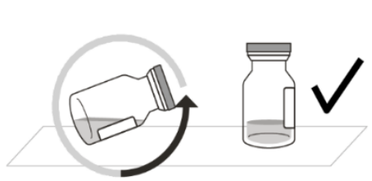


Figure B

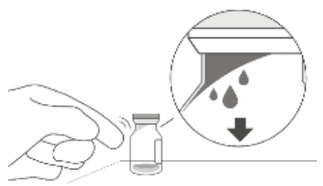


Figure C

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

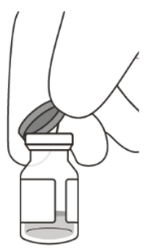


Figure D

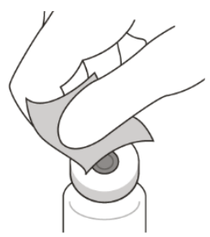


Figure E

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**).

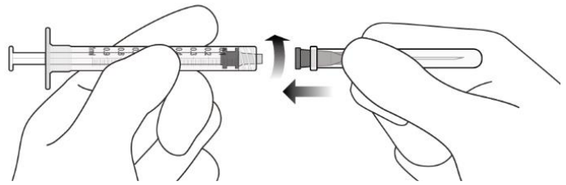


Figure F

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**).

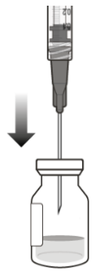


Figure G

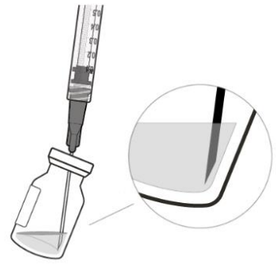


Figure H

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.

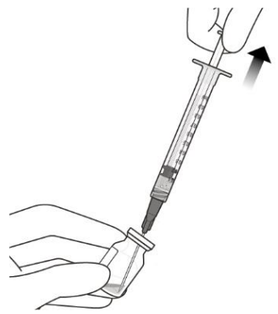


Figure I

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**).

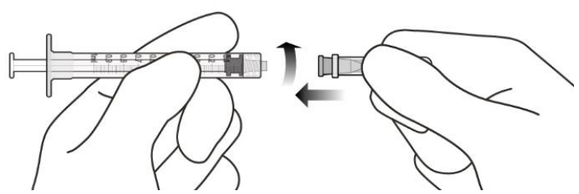


Figure J

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**).

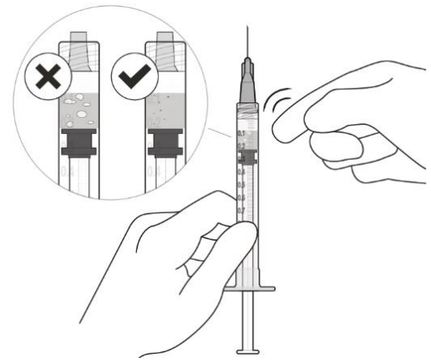


Figure K

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.

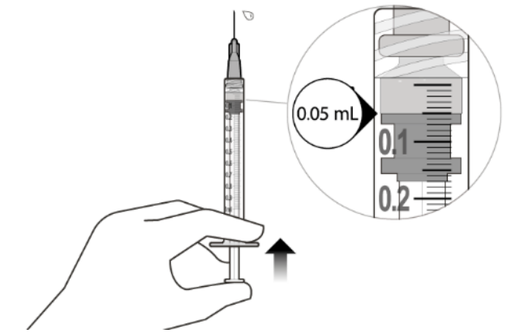


Figure L

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.