Faricimab (visual impairment due to diabetic macular oedema) –

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BCVA	best-corrected visual acuity
DMO	diabetic macular oedema
ETDRS	Early Treatment Diabetic Retinopathy Study
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NEI VFQ-25	National Eye Institute Visual Function Questionnaire-25
PTI	personalized treatment interval
Q8W	at 8-week intervals
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug faricimab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 14 October 2022.

Research question

The aim of this report was to assess the added benefit of faricimab in comparison with ranibizumab or aflibercept as the appropriate comparator therapy (ACT) in adults with visual impairment due to diabetic macular oedema (DMO).

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of faricimab

Therapeutic indication	**ACT**[a]
Visual impairment due to DMO[b] in adults	Ranibizumab or **aflibercept**
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. b. Patients with visual impairment due to DMO are assumed to exhibit foveal involvement. The presence of clinically significant macular oedema as per ETDRS criteria is assumed. ACT: appropriate comparator therapy; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study; G-BA: Federal Joint Committee	

The company followed the G-BA's specification by identifying aflibercept as the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for deriving added benefit.

Study pool and study design

The study pool for the benefit assessment of faricimab in comparison with aflibercept comprised the 2 studies RHINE and YOSEMITE. Both studies are double-blind RCTs comparing faricimab versus aflibercept.

The studies enrolled adult patients with type 1 or type 2 diabetes mellitus, a glycosylated haemoglobin (HbA1c) of ≤ 10% within 2 months prior to treatment start (Day 1), and visual impairment due to DMO. In each patient, 1 eye was selected as the study eye. The best-corrected visual acuity (BCVA) of the study eye had to be between 73 and 25 ETDRS letters at

a distance of 4 meters using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts. In addition, the study eye had to exhibit retinal oedema involving the fovea with a central subfield thickness of ≥ 325 µm or ≥ 315 µm.

A total of 951 patients in the RHINE study and 940 patients in the YOSEMITE study were randomized to the following study arms at a 1:1:1 ratio:

- faricimab in 4-week intervals until Week 20, followed by 8-week intervals (Q8W)
- faricimab in 4-week intervals until at least Week 12, followed by personalized treatment intervals (PTI)
- aflibercept

In the faricimab-PTI arm of the 2 studies, patients received faricimab in accordance with the specifications of the Summary of Product Characteristics (SPC). The faricimab-Q8W arm is irrelevant for the present benefit assessment. According to the aflibercept SPC, aflibercept treatment may be individualized after the first 12 months of treatment using a treat-and-extend dosing regimen based on functional and/or morphological findings. However, neither of the studies provided for such individualization of dosing intervals after Year 1 of aflibercept treatment.

The primary outcome in the RHINE and YOSEMITE studies was change in BCVA from baseline at Year 1. Patient-relevant outcomes on morbidity, health-related quality of life, and side effects were additionally recorded in both studies.

Dates of analysis

For both studies, Appendix 4-G of the dossier's Module 4A provides data from the primary analysis at Year 1 and Module 4A shows data from the final analysis at Year 2. In departure from the company's approach, the present benefit assessment used only analyses at Year 1 because neither study provided for flexibilization of the aflibercept treatment regimen as recommended by the SPC after the 1st year of treatment; the same did not apply to the faricimab-PTI arm, leading to inequalities between the study arms.

Risk of bias

The risk of bias across outcomes was rated as low for both studies.

The outcome-specific risk of bias was likewise rated as low.

Based on the available data, no more than proof, e.g. of an added benefit, can be determined for all outcomes.

Results

Mortality

All-cause mortality

For the outcome of all-cause mortality, the meta-analysis of the RHINE and YOSEMITE studies does not show any statistically significant differences between treatment groups. This resulted in no hint of an added benefit of faricimab in comparison with aflibercept; an added benefit is therefore not proven.

Morbidity

BCVA

For the outcome of BCVA (responder analysis on improvement by ≥ 10 ETDRS letters), the metaanalysis of the RHINE and YOSEMITE studies showed no statistically significant differences between treatment groups. This results in no hint of an added benefit of faricimab in comparison with aflibercept; an added benefit is therefore not proven.

Health status (National Eye Institute Visual Function Questionnaire-25 [NEI VFQ-25], general health subscale)

For the outcome of health status (surveyed via NEI VFQ-25 general health subscale), the metaanalysis of the RHINE and YOSEMITE studies does not show any statistically significant differences between treatment groups. This results in no hint of an added benefit of faricimab in comparison with aflibercept; an added benefit is therefore not proven.

Health-related quality of life

NEI VFQ-25 (summary score)

For the outcome of health-related quality of life (surveyed via NEI VFQ-25 summary score), the metaanalysis of the RHINE and YOSEMITE studies does not show any statistically significant differences between treatment groups. This results in no hint of an added benefit of faricimab in comparison with aflibercept; an added benefit is therefore not proven.

Side effects

Serious AEs (SAEs), discontinuation due to AEs, ocular AEs, and ocular SAEs

The metaanalysis of the RHINE and YOSEMITE studies showed no statistically significant differences between treatment groups for any of the outcomes of SAEs, discontinuation due to AEs, ocular AEs, or ocular SAEs. Hence, there is no hint of greater or lesser harm from faricimab in comparison with aflibercept for any of them; greater or lesser harm is therefore not proven.

Supplementary note on the appropriate comparator therapy

The aflibercept SPC was revised in December 2022. Aflibercept treatment is initiated with 5 consecutive monthly injections, followed by 1 injection every 2 months. As per the revised SPC, the physician may subsequently, based on functional and/or morphological findings, either maintain the 2-month treatment interval or individualize it using a treat-and-extend dosing regimen with 2-week adjustments. The original SPC allowed flexibilization of the treatment interval only after 12 months. The present benefit assessment is based on the original ACT.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the extent and probability of added benefit of the drug faricimab compared with the ACT is assessed as follows:

Overall, neither favourable nor unfavourable effects were found for faricimab in comparison with aflibercept.

In summary, there is no hint of added benefit of faricimab versus aflibercept for adults with visual impairment due to DMO; an added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of added benefit of faricimab.

Table 3: Faricimab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Visual impairment due to DMO[b] in adults	Ranibizumab or **aflibercept**	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Patients with visual impairment due to DMO are assumed to have foveal involvement. The presence of clinically significant macular oedema according to the ETDRS criteria is assumed.

ACT: appropriate comparator therapy; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study; G-BA: Federal Joint Committee

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

The approach for deriving an overall conclusion on added benefit constitutes a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report was to assess the added benefit of faricimab in comparison with ranibizumab or aflibercept as the ACT in adults with visual impairment due to DMO.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of faricimab

Therapeutic indication	**ACT**[a]
Visual impairment due to DMO[b] in adults	Ranibizumab or **aflibercept**

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Patients with visual impairment due to DMO are assumed to have foveal involvement. The presence of clinically significant macular oedema according to the ETDRS criteria is assumed.

ACT: appropriate comparator therapy; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study; G-BA: Federal Joint Committee

The company followed the G-BA's specification by identifying aflibercept as the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for deriving added benefit. This does not correspond to the inclusion criteria of the company, which imposed no restrictions regarding study duration.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on faricimab (status: 8 August 2022)
- bibliographical literature search on faricimab (last search on 8 August 2022)
- search in trial registries / trial results databases for studies on faricimab (last search on 8 August 2022)
- search on the G-BA website for faricimab (last search on 8 August 2022)

To check the completeness of the study pool:

- search in trial registries for studies on faricimab (last search on 25 October 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

I 3.1 Studies included

The studies listed in Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: faricimab versus aflibercept

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
GR40398 (RHINE[c])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7]
GR40349 (YOSEMITE[c])	Yes	Yes	No	Yes [8,9]	Yes [10-12]	Yes [7]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

The study pool for the benefit assessment of faricimab versus the ACT of aflibercept consists of the RHINE and YOSEMITE studies and coincides with the company's study pool.

I 3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: faricimab versus aflibercept (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
RHINE	RCT, double-blind, parallel-group	Adult patients (≥ 18 years) with type 1 or type 2 diabetes mellitus (HbA1c ≤ 10% within 2 months prior to treatment start) and visual impairment due to DMO[b]	▪ Faricimab 6 mg Q8W (N = 317)[c] ▪ Faricimab 6 mg PTI (N = 319) ▪ Aflibercept (N = 315)	▪ Screening: up to 28 days ▪ Treatment: 96 weeks ▪ Observation: 4 weeks	174 study centres in: Argentina, Australia, Brazil, Canada, China, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Italy, Poland, Portugal, Russia, Singapore, South Korea, Spain, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, United States 10/2018 – 8/2021 Data cut-off: ▪ Year 1: 19/10/2020 (primary analysis) ▪ Year 2: 28/10/2021 (final analysis after end of study)	Primary: change in BCVA at Year 1 vs. baseline Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, direct comparison: faricimab versus aflibercept (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
YOSEMITE	see RHINE	see RHINE	▪ Faricimab 6 mg Q8W (N = 315)[c] ▪ Faricimab 6 mg PTI (N = 313) ▪ Aflibercept (N = 312)	see RHINE	179 study centres in: Austria, Bulgaria, France, Germany, Hungary, Israel, Italy, Japan, Mexico, Peru, Poland, Russia, Slovakia, Spain, Turkey, United States 09/2018 – 09/2021 Data cut-off: ▪ Year 1: 20/10/2020 (primary analysis) ▪ Year 2: 1/11/2021 (final analysis after end of study)	see RHINE

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Concerning the study eye: visual impairment due to DMO with
- retinal oedema involving the fovea with a CST ≥ 325 µm in Spectralis SD-OCT or ≥ 315 µm in Cirrus SD-OCT or Topcon SD-OCT at screening.
- BCVA between 73 and 25 ETDRS letters (inclusive) using ETDRS vision charts at a distance of 4 meters (approximately corresponds to a Snellen equivalent of 20/40 to 20/320) on Day 1

  If both eyes were suitable, the eye with the poorer visual acuity at screening was chosen as the study eye unless the investigator deemed the other eye to be more suitable for treatment with the study medication.

c. The arm is irrelevant for the assessment and is disregarded in the following tables.

AE: adverse event; BCVA: best-corrected visual acuity; CST: central subfield thickness; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study; N: number of randomised patients; PTI: personalized treatment interval; Q8W: every 8 weeks; RCT: randomized controlled trial; SD-OCT: Spectral Domain-Optical Coherence Tomography; VEGF: vascular endothelial growth factor

Table 7: Characteristics of the intervention – RCT, direct comparison: faricimab versus aflibercept (multipage table)

Study	Intervention	Comparison
RHINE	Faricimab 6 mg intravitreal injection ▪ Set-up phase: 4 times 1 injection every 4 weeks ▪ Maintenance phase: individualized dosing interval[a] + Sham injections according to aflibercept treatment regimen	Aflibercept 2 mg intravitreal injection ▪ Set-up phase: 5 times 1 injection every 4 weeks ▪ Maintenance phase: 1 injection every 8 weeks + Sham injections according to faricimab treatment regimen
	Dose adjustments ▪ Treatment interruptions due to AEs permitted	
	Disallowed pretreatment ▪ Systemic therapies for promoting angiogenesis within 3 months or 5 half-lives before Day 1 ▪ Start of antidiabetic therapy within 3 months before Day 1 ▪ Study eye: ▫ intravitreal anti-VEGF therapy within 3 months before Day 1 (patients with prior treatment) or any intravitreal anti-VEGF therapy before Day 1 (patients without prior treatment) ▫ PRP, laser coagulation of the macula, any cataract surgery or steroid treatment of complications of cataract surgery or YAG-laser capsulotomy within 3 months prior to Day 1 ▫ any other intraocular surgery ▫ intraocular or periocular corticosteroids and drug-loaded intravitreal implants within 6 months prior to Day 1 ▫ any fluocinolone acetonide intravitreal implants ▫ treatment of other retinal diseases which may lead to macular oedema	
	Concomitant treatment <u>Allowed</u> ▪ Non-study eye: anti-VEGF therapy at the investigator's discretion <u>Disallowed</u> ▪ Study eye: ▫ intravitreal anti-VEGF therapy (except study medication) ▫ intravitreal, periocular, or (in chronic ocular diseases) topical corticosteroids ▫ steroid implants ▫ micropulse laser treatment and focal/grid laser coagulation ▫ photodynamic therapy with verteporfin ▪ Systemic: ▫ anti-VEGF therapy ▫ medications known to potentially induce macular oedema (fingolimod, tamoxifen) ▫ other experimental therapies (except those containing vitamins and minerals)	
YOSEMITE	see RHINE	

a. After initial extension of the dosing interval to 8 weeks, it was possible to further extend the interval based on CST and/or visual acuity assessment in 4-week adjustments to a maximum of 16 weeks, keep it unchanged, or shorten the interval to a minimum of 4 weeks.

AE: adverse event; CST: central subfield thickness; PRP: panretinal photocoagulation; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; YAG: yttrium aluminium garnet

Study pool and study design

For its benefit assessment, the company submitted the RHINE and YOSEMITE studies. The RHINE and YOSEMITE studies have an identical design and are described together below, unless otherwise stated. Both studies are double-blind RCTs comparing faricimab versus aflibercept.

The studies enrolled adult patients with type 1 or type 2 diabetes mellitus and HbA1c ≤ 10% within 2 months prior to treatment start (Day 1) and visual impairment due to DMO. In each patient, 1 eye was selected as the study eye. The BCVA of the study eye had to be between 73 and 25 ETDRS letters using ETDRS vision charts at a distance of 4 meters. In addition, the study eye had to exhibit retinal oedema involving the fovea with a central subfield thickness of ≥ 325 µm or ≥ 315 µm (see Table 6). In participants where both eyes were suitable, the eye with the inferior visual acuity was selected as the study eye. However, the investigator had the option of choosing the eye with the better visual acuity if that eye was deemed better suited for treatment with the study medication. The company's documents show that in about 10% of patients (RHINE) or 9% of patients (YOSEMITE), both eyes met the studies' inclusion criteria and that in about one-third of these cases, the eye with the better visual acuity was chosen. However, the company does not cite the reasons for deciding against the eye with inferior visual acuity.

Enrolled were patients whose study eye had prior anti-VEGF therapy as well as patients without prior anti-VEGF therapy. However, intravitreal anti-VEGF therapy was disallowed within 3 months before Day 1. In both studies, the percentage of patients who had already received anti-VEGF therapy was to equal a minimum of 10% and a maximum of 25%.

A total of 951 patients in the RHINE study and 940 patients in the YOSEMITE study were randomized to the following study arms at a 1:1:1 ratio:

- faricimab in 4-week intervals until Week 20, followed by Q8W
- faricimab in 4-week intervals until at least Week 12, followed by PTI
- aflibercept

In both studies, randomization was stratified by BCVA on Day 1 (< 64 ETDRS letters versus ≥ 64 ETDRS letters), prior treatment with intravitreal anti-VEGF therapies (yes versus no), and region (USA/Canada versus Asia versus rest of the world).

In both studies' faricimab-PTI arms, patients received faricimab in accordance with SPC specifications [13]. The faricimab-Q8W arm is irrelevant for the present benefit assessment because it did not provide for a flexible treat-and-extend dosing regimen on the basis of a

medical assessment of anatomic and/or visual findings as stipulated by the SPC to be initiated after 4 initial injections at monthly intervals. This concurs with the company's assessment.

The RHINE and YOSEMITE studies each initiated aflibercept treatment with 5 consecutive monthly injections, followed by 1 injection every 2 months. As per aflibercept SPC [14], aflibercept treatment may be individualized after the first 12 months of treatment, using a treat-and-extend dosing regimen based on functional and/or morphological findings. Neither study provided for such individualized aflibercept treatment intervals after the 1st year of treatment.

Primary outcome in the RHINE and YOSEMITE studies was change from baseline in BCVA at Year 1. Patient-relevant outcomes on morbidity, health-related quality of life, and side effects were additionally recorded in both studies.

Dates of analysis

Results on 2 data cut-offs are available for both studies:

- data cut-off 1 (19 October 2020 [RHINE], 20 October 2020 [YOSEMITE]): predefined analysis of the primary outcome; planned to occur when all patients have either completed 56 weeks of the study or discontinued participation prior to this time
- data cut-off 2 (28 October 2021 [RHINE], 1 November 2021 [YOSEMITE]): predefined final analysis; planned to occur when all patients have either completed 100 weeks of the study or discontinued participation prior to this time

Appendix 4-G of Module 4A provides data of the primary analysis at Year 1, and Module 4A, data of the final analysis at Year 2. In deviation from the company's approach, the present benefit assessment uses only analyses at Year 1.

The company presumes that, in both studies, the use of aflibercept every 8 weeks after the 1st year of treatment meets the specifications of the SPC because, in its view, flexibilization of the treatment interval represents merely a "possible" option and the treat-and-extend regimen has not been shown to be superior to 8-week treatment intervals. In its arguments, the company cites the VIOLET study [15], a 100-week randomized, open-label, active control study investigating the non-inferiority of the treat-and-extend and *pro re nata* dosing regimens in comparison with the Q8W dosage of aflibercept in the treatment of DMO following 1-year treatment with continuous injection intervals. On the basis of this study's results, the company concludes that the effectiveness and tolerability of the treat-and-extend and Q8W regimens is sufficiently comparable in the 2nd and 3rd year of aflibercept treatment. For assessing added benefit, the company therefore presents the results of the final analyses at Year 2 in the dossier's Module 4A. The company reports the results of the primary analyses

of Year 1 only in the dossier's Appendix 4-G and disregards them in its derivation of added benefit. This approach is inappropriate for the reasons stated below.

In case of non-inferiority of the treat-and-extend regimen to Q8W dosage, the group of authors concludes that patients prefer flexibilization because it is associated with longer injection intervals and fewer doctor visits. This conclusion is supported by the justification paper for the G-BA's decision on brolucizumab [16] which states that according to clinical practitioners, an individualized injection interval based on disease severity is the goal in routine care. Further, unlike the aflibercept arm, the faricimab-PTI arm offered a more flexible dosing regimen after only Week 12, resulting in disparities between the study arms. In deviation from the company's approach, the present benefit assessment therefore disregards any comparative (primary) analyses at any time after Year 1.

For both studies, results on Year 1 are available from analyses of the 1st data cut-off (primary analysis) and on the 2nd data cut-off (final analysis) (see Table 6). The results in the dossier's Appendix 4-G, where the company presents analyses for Year 1 at the 2nd data cut-off, exhibit minor deviations from the 2 study reports containing the analyses of Year 1 from the 1st data cut-off. For the present benefit assessment, the more recent results from the 2nd data cut-off for Year 1 were used.

Characteristics of the study populations

Table 8 presents the characteristics of patients in the RHINE and YOSEMITE studies.

Table 8: Characteristics of the study populations as well as discontinuation of the study/therapy – RCT, direct comparison: faricimab versus aflibercept

Study	RHINE		YOSEMITE	
Characteristic Category	Faricimab	Aflibercept	Faricimab	Aflibercept
	N[a] = 319	N[a] = 315	N[a] = 313	N[a] = 312
Age [years], mean (SD)	62 (10)	62 (10)	63 (10)	62 (10)
Sex [f/m], %	38/62	41/59	37/63	43/57
Ancestry, n (%)				
White	249 (78)	253 (80)	240 (77)	253 (81)
Black	23 (7)	24 (8)	25 (8)	12 (4)
Asian	36 (11)	32 (10)	26 (8)	27 (9)
Others[b]	1 (< 1)	1 (< 1)	6 (2)	10 (3)
Unknown	10 (3)	5 (2)	16 (5)	10 (3)
Type of diabetes, n (%)				
Type 1	19 (6)	17 (5)	16 (5)	13 (4)
Type 2	300 (94)	298 (95)	299 (96)	299 (96)
HbA1c [%], mean (SD)	7.7 (1.2)	7.7 (1.2)	7.6 (1.1)	7.6 (1.1)
Disease duration: time since DMO diagnosis [months]	N = 277	N = 273	N = 292	N = 296
Mean (SD)	20.7 (33.0)	20.3 (37.1)	17.6 (36.2)	17.5 (27.6)
Median [min; max]	6.6 [0; 242]	6.8 [0; 365]	2.3 [0; 304]	3.4 [0; 180]
BCVA [ETDRS letters], mean (SD)	62.5 (9.3)	62.1 (9.4)	61.9 (10.2)	62.2 (9.5)
BCVA category, n (%)				
≤ 38 ETDRS letters	11 (3)	9 (3)	12 (4)	12 (4)
39 to 63 ETDRS letters	132 (41)	132 (42)	126 (40)	132 (42)
≥ 64 ETDRS letters	174 (55)	174 (55)	175 (56)	168 (54)
CST[c] [µm], mean (SD)	471.3 (127.0)	477.5 (129.3)	485.8 (130.8)	484.4 (131.1)
Prior intravitreal anti-VEGF therapy[d], n (%)	65 (20)	67 (21)	68 (22)	70 (22)
Treatment discontinuation by Week 56 n (%)	11 (3)	19 (6)	30 (10)	26 (8)
Study discontinuation by Week 56, n (%)	7 (2)	16 (5)	24 (8)	20 (6)

a. Number of randomized patients. Values which are based on other patient numbers are marked in the corresponding row if the deviation is relevant.
b. Institute's calculation, sum of the categories of Native American or Alaska Native, Native Hawaiian or Other Pacific Islander, and Mixed.
c. Defined as the distance between the inner limiting membrane and Bruch's membrane.
d. Comprises both approved drugs and those not approved for the indication of DMO (aflibercept, bevacizumab, pegaptanib sodium, and ranibizumab).

BCVA: best corrected visual acuity; CST: central subfield thickness; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study; f: female; HbA1c: glycosylated haemoglobin; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; VEGF: vascular endothelial growth factor

Demographic characteristics are largely comparable between the RHINE and YOSEMITE studies as well as between their study arms. The majority of patients were of White ancestry, and the average age was over 62 years. Nearly 40% of patients were female. The majority patients (over 90%) had type 2 diabetes mellitus. On average, patients' HbA1c value was 7.6 to 7.7%.

The median time since DMO diagnosis was 6.6 or 6.8 months in the RHINE study, higher than in the YOSEMITE study at 2.3 and 3.4 months. More than half of participants (55%) had a BCVA of at least 64 ETDRS letters. About 21% of participants had received prior intravitreal anti-VEGF therapy.

The percentage of participants with treatment discontinuation as well as the percentage of those who dropped out of the study was ≤ 10% in each of the study arms.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: faricimab versus aflibercept

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
RHINE	Yes	Yes	Yes	No[a]	Yes	Yes	Low
YOSEMITE	Yes	Yes	Yes	No[a]	Yes	Yes	Low

a. Treatment administration was unblinded; outcome survey was blinded.

RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for both studies.

Transferability of the study results to the German health care context

In the company's opinion, the results of the RHINE and YOSEMITE studies are transferable to the German health care context. The company reasons that, firstly, the studies enrolled predominantly patients of White ancestry from North America and Europe. Secondly, the company argues that the study populations are comparable to the patient population in Germany in terms of their demographic and clinical characteristics (age, loss of BCVA, and increase in central subfield thickness). Furthermore, disease activity was assessed based on

anatomic and/or visual criteria which, according to the company, likewise match those found in the German healthcare context.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - BCVA (measured using ETDRS vision charts)
  - health status (surveyed by means of the NEI VFQ-25, subscale general health status)
- Health-related quality of life
  - health-related quality of life (recorded using NEI VFQ-25)
- Side effects
  - SAEs
  - discontinuation due to adverse events (AEs)
  - ocular AEs
  - ocular SAEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows the outcomes for which data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: faricimab versus aflibercept

Study	Outcomes								
	All-cause mortality	Visual acuity (BCVA)[a]	Health status (NEI VFQ-25, subscale of general health status)	Health-related quality of life (NEI VFQ-25)	SAEs[b]	Discontinuation due to AEs[b]	Severe AEs[a, b]	Ocular SAEs[a, b]	Further specific AEs[c]
RHINE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
YOSEMITE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

a. Result refers to the study eye.
b. Includes events due to the underlying illness. Given the available data, however, the analyses are usable because the disease-related events included in the respective analyses presumably do not impact study results in a relevant manner.
c. No further specific AEs were identified based on the AEs occurring in the relevant studies.

AE: adverse event; BCVA: best-corrected visual acuity; MedDRA: Medical Dictionary for Regulatory Activities; NEI VFQ-25: National Eye Institute Function Questionnaire-25; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event

Notes on the included outcomes and analyses

BCVA

In both studies, BCVA was measured using ETDRS vision charts at an initial distance of 4 meters. A vision chart consists of 14 rows of eye test characters with 5 letters each and is thus made up of a total of 70 letters. The size of the letters decreases with each row.

At a distance of 4 meters, the BCVA results from the number of correctly read letters plus 30; at a distance of 1 meter, the BCVA equals the number of correctly read letters. BCVA scores can range from 0 to 100, with higher scores indicating better visual acuity.

The company's dossier presents both continuous analyses and responder analyses on BCVA improvement and prevention of deterioration. Of primary relevance is an analysis of BCVA improvement because, according to comments on the treatment of DMO [17], treatment in the present therapeutic indication with intravitreally administered drugs such as faricimab or aflibercept should be limited to cases where a favourable influence on functional and/or morphological findings can be expected. In line with the reasons described in the ocriplasmin benefit assessments [18,19], the responder analysis of improvement by ≥ 10 ETDRS letters (corresponds to 2 rows) was used for the present benefit assessment. The responder analysis

of improvement by ≥ 15 ETDRS letters (corresponds to 3 rows) is presented as supplementary information.

National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25)

The NEI VFQ-25 is a questionnaire for measuring vision-related quality of life, which consists of a total of 26 items and 12 subscales [20]. A total of 25 of these items (11 subscales) query about visual acuity, while 1 item (1 subscale) queries general health.

The values for all items are transformed to a score of 0 to 100, and for each subscale, a mean score is calculated from the subscale items. Ultimately, the sum score is calculated from the mean of the averaged subscale scores. The subscale on general health is disregarded in this process. The NEI VFQ-25 sum score can range from 0 to 100, with higher scores indicating better vision-related quality of life.

The company presents responder analyses of improvement of the NEI VFQ-25 sum score and the 12 subscales by ≥ 15 points each. In Module 4A, the company explains that patients were rated as responders if they met the response criterion at a minimum of 1 visit up to Week 56. During this period, the NEI VFQ-25 was surveyed on Day 1, at Week 24, and at Week 52, or at the time of study dropout. Hence, none of the available responder analyses defined responders as only patients who, at Week 52, had exhibited an improvement in the sum score or subscale scores by ≥ 15 points. The present assessment therefore uses the continuous analyses which the company presents as supplementary information in Appendix 4-G. Like the continuous analyses, the responder analyses show no statistically significant difference between treatment groups in either case.

In departure from the company's approach, the general health subscale (1 item) is allocated to the morbidity category.

Side effects

For the overall rates of AEs and SAEs, the company's dossier does not present any additional AE analyses disregarding disease-related events (e.g. PT diabetic retinal oedema) as required by the dossier template [21]. Likewise, the company did not present any analyses which excluded events due to the underlying illness when calculating total rates of ocular AEs and ocular SAEs. The total rates of AEs including events due to the underlying illness are used in the present benefit assessment because given the available evidence, the disease-related events included in these analyses presumably do not have any relevant impact on the study results.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: faricimab versus aflibercept

Study	Study level	Outcomes								
		All-cause mortality	Visual acuity (BCVA)[a]	Health status (NEI VFQ-25, subscale of general health status)	Health-related quality of life (NEI VFQ-25)	SAEs	Discontinuation due to AEs	Ocular AEs[a]	Ocular SAEs[a]	Further specific AEs
RHINE	L	L	L	L	L	L	L	L	L	–
YOSEMITE	L	L	L	L	L	L	L	L	L	–

a. Result refers to the study eye.

AE: adverse event; BCVA: best-corrected visual acuity; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; NEI VFQ-25: National Eye Institute Function Questionnaire-25; PT: Preferred Term; RCT: randomized controlled trial SAE: serious adverse event

The risk of bias for the results on all outcomes was rated as low.

I 4.3 Results

Table 12 and Table 13 summarize the results on the comparison of faricimab versus aflibercept in adults with visual impairment due to DMO. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: faricimab versus aflibercept (multipage table)

Outcome category Outcome Study	Faricimab N	Faricimab Patients with event n (%)	Aflibercept N	Aflibercept Patients with event n (%)	Faricimab vs. aflibercept RR [95% CI][a]; p-value
Week 56					
Mortality					
All-cause mortality					
RHINE	319	0 (0)	314	5 (1.6)	0 [0; NC]; 0.024[b]
YOSEMITE	313	9 (2.9)	311	4 (1.3)	2.24 [0.70; 7.18]; 0.212[b]
Total					0.99 [0.40; 2.47][c]; 0.981[d]
Morbidity					
BCVA[e] (improvement by ≥ 10 ETDRS letters[f])					
RHINE	294	155 (52.7)	279	151 (54.1)	0.97 [0.84; 1.12]; 0.791[b]
YOSEMITE	276	161 (58.3)	276	159 (57.6)	1.03 [0.90; 1.18]; 0.916[b]
Total					1.00 [0.91; 1.10]; 0.916[d]
BCVA[e] (improvement by ≥ 15 ETDRS letters[f]), provided as supplementary information					
RHINE	*294*	*83 (28.2)*	*279*	*85 (30.5)*	*0.97 [0.76; 1.23]; 0.600[b]*
YOSEMITE	*276*	*98 (35.5)*	*276*	*88 (31.9)*	*1.10 [0.88; 1.37]; 0.530[b]*
Total					*1.04 [0.88; 1.22]; 0.799[d]*
Side effects					
AEs[g] (supplementary information)					
RHINE	319	234 (73.4)	314	246 (78.3)	–
YOSEMITE	313	255 (81.5)	311	245 (78.8)	–
SAEs[g]					
RHINE	319	52 (16.3)	314	58 (18.5)	0.88 [0.63; 1.24]; 0.533[b]
YOSEMITE	313	77 (24.6)	311	58 (18.6)	1.32 [0.97; 1.79]; 0.072[b]
Total					1.10 [0.88; 1.38]; 0.408[d]
Discontinuation due to AEs					
RHINE[g]	319	4 (1.3)	314	3 (1.0)	1.31 [0.30; 5.82]; 0.804[b]
YOSEMITE	313	8 (2.6)	311	3 (1.0)	2.65 [0.71; 9.89]; 0.140[b]
Total					1.98 [0.75; 5.24]; 0.162[d]
Ocular AEs[e, g]					
RHINE	319	116 (36.4)	314	109 (34.7)	1.05 [0.85; 1.29]; 0.712[b]
YOSEMITE	313	105 (33.5)	311	103 (33.1)	1.01 [0.81; 1.26]; 0.937[b]
Total					1.03 [0.89; 1.20]; 0.696[d]

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: faricimab versus aflibercept (multipage table)

Outcome category Outcome Study	Faricimab N	Faricimab Patients with event n (%)	Aflibercept N	Aflibercept Patients with event n (%)	Faricimab vs. aflibercept RR [95% CI][a]; p-value
Ocular SAEs[e,g]					
RHINE	319	9 (2.8)	314	6 (1.9)	1.48 [0.53; 4.10]; 0.533[b]
YOSEMITE	313	9 (2.9)	311	2 (0.6)	4.47 [0.97; 20.53]; 0.038[b,h]
Total					2.23 [0.97; 5.08]; 0.051[d]

a. RR and CI from regression model; for morbidity outcomes stratified by BCVA at Day 1 (< 64 vs. ≥ 64 ETDRS letters), prior treatment with intravitreal anti-VEGF therapies (yes vs. no), and region (USA/Canada vs. Asia/rest of the world); for pooled analysis, each additionally stratified by study.
b. Institute's calculation, unconditional exact test (CSZ method according to [22]).
c. Despite statistically significant heterogeneity (p = 0.003 [likelihood ratio test]), the common effect estimator is presented given the available data.
d. Calculation from IPD metaanalysis with the study factor as a fixed effect (see footnote "a" on the model); p-value: Cochrane-Mantel-Haenszel test.
e. Refers to the study eye.
f. Proportion of patients with an increase in BCVA by ≥ 10 ETDRS letters (or by ≥ 15 ETDRS letters, presented as supplementary information) from baseline shown as an average for Weeks 48, 52, and 56 (scale range of 0 to 100). The analysis disregarded observations following a COVID-19-related event.
g. Includes events of the underlying illness.
h. Discrepancy between CI and p-value due to different calculation methods.

AE: adverse event; BCVA: best-corrected visual acuity; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ETDRS: Early Treatment Diabetic Retinopathy Study; IPD: individual patient data; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VEGF: vascular endothelial growth factor

Table 13: Results (morbidity, health-related quality of life) – RCT, direct comparison: faricimab versus aflibercept (multipage table)

Outcome category Outcome	Faricimab			Aflibercept			Faricimab vs. aflibercept
Study	N[a]	Values at baseline mean (SD)	Change at Week 52 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at Week 52 mean[b] (SE)	MD [95% CI][b]; p-value
Morbidity							
NEI VFQ-25[c]							
General health subscale							
RHINE	275	45.38 (21.54)	4.64 (1.09)	259	44.25 (21.34)	6.52 (1.12)	-1.88 [-4.95; 1.19]; ND
YOSEMITE	256	47.02 (19.22)	3.44 (1.17)	248	46.19 (19.86)	4.80 (1.18)	-1.36 [-4.61; 1.90]; ND
Total							-1.65 [-3.88; 0.59][d]; ND
Health-related quality of life							
NEI VFQ-25[c]							
Sum score							
RHINE	275	74.33 (17.47)	7.07 (0.66)	259	74.67 (18.54)	7.51 (0.68)	-0.44 [-2.31; 1.43]; ND
YOSEMITE	256	72.83 (18.15)	7.96 (0.71)	248	73.97 (17.70)	7.93 (0.71)	0.03 [-1.94; 2.00]; ND
Total							-0.20 [-1.55; 1.16][d]; ND
General vision subscale							
RHINE	275	60.88 (16.54)	9.98 (0.78)	259	60.64 (17.09)	10.03 (0.80)	-0.05 [-2.25; 2.15]
YOSEMITE	256	60.39 (16.33)	10.58 (0.80)	248	60.97 (16.31)	11.04 (0.81)	-0.46 [-2.68; 1.77]
Total							-0.25 [-1.81; 1.31][d]
Ocular pain subscale							
RHINE	275	81.35 (22.41)	4.61 (0.92)	259	83.67 (20.83)	4.64 (0.95)	-0.03 [-2.63; 2.56]
YOSEMITE	256	81.57 (20.38)	4.89 (0.93)	248	83.00 (20.06)	4.48 (0.95)	0.40 [-2.21; 3.01]
Total							0.19 [-1.66; 2.03][d]

Table 13: Results (morbidity, health-related quality of life) – RCT, direct comparison: faricimab versus aflibercept (multipage table)

Outcome category Outcome	Faricimab			Aflibercept			Faricimab vs. aflibercept
Study	N[a]	Values at baseline mean (SD)	Change at Week 52 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at Week 52 mean[b] (SE)	MD [95% CI][b]; p-value
Near vision subscale							
RHINE	274	64.66 (23.98)	10.66 (1.04)	259	65.19 (24.26)	9.89 (1.07)	0.77 [-2.15; 3.69]
YOSEMITE	256	63.35 (23.48)	10.28 (1.08)	248	63.47 (23.90)	10.74 (1.10)	-0.46 [-3.49; 2.57]
Total							0.19 [-1.91; 2.30][d]
Distance vision subscale							
RHINE	274	73.52 (21.86)	8.67 (0.94)	259	74.47 (23.53)	7.96 (0.96)	0.71 [-1.93; 3.35]
YOSEMITE	256	71.18 (22.04)	9.13 (0.98)	248	71.44 (22.60)	8.50 (0.99)	0.63 [-2.11; 3.36]
Total							0.67 [-1.24; 2.57][d]
Social functioning subscale							
RHINE	275	86.17 (18.50)	3.94 (0.86)	259	86.50 (19.47)	4.18 (0.89)	-0.24 [-2.67; 2.20]
YOSEMITE	256	84.31 (20.30)	5.53 (0.89)	248	83.69 (21.08)	4.76 (0.90)	0.77 [-1.71; 3.25]
Total							0.26 [-1.48; 2.00][d]
Well-being/distress subscale							
RHINE	275	62.74 (25.73)	10.88 (1.11)	259	62.84 (29.18)	11.77 (1.14)	-0.89 [-4.00; 2.23]
YOSEMITE	256	62.48 (27.01)	12.40 (1.18)	248	63.98 (26.13)	13.28 (1.19)	-0.88 [-4.18; 2.41]
Total							-0.86 [-3.12; 1.40][d]
Social functioning subscale							
RHINE	275	67.40 (27.63)	8.96 (1.29)	259	64.78 (31.64)	9.44 (1.32)	-0.48 [-4.11; 3.15]
YOSEMITE	256	65.60 (29.08)	11.18 (1.38)	248	67.45 (29.70)	11.12 (1.40)	0.07 [-3.80; 3.94]
Total							-0.17 [-2.82; 2.48][d]
Subscale: dependency on others							
RHINE	275	78.94 (28.04)	6.29 (1.15)	259	78.81 (29.36)	7.48 (1.18)	-1.19 [-4.42; 2.04]
YOSEMITE	256	78.63 (27.27)	7.70 (1.19)	248	79.60 (26.73)	7.69 (1.20)	0.02 [-3.31; 3.34]
Total							-0.59 [-2.90; 1.72][d]

Table 13: Results (morbidity, health-related quality of life) – RCT, direct comparison: faricimab versus aflibercept (multipage table)

Outcome category Outcome Study	Faricimab			Aflibercept			Faricimab vs. aflibercept
	N[a]	Values at baseline mean (SD)	Change at Week 52 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at Week 52 mean[b] (SE)	MD [95% CI][b]; p-value
Subscale for vehicular driving problems							
RHINE	No usable data[e]						
YOSEMITE	No usable data[e]						
Colour vision subscale							
RHINE	266	92.89 (15.22)	1.74 (0.75)	256	92.60 (16.36)	3.43 (0.77)	-1.69 [-3.80; 0.41]
YOSEMITE	256	91.10 (17.61)	2.69 (0.8)	248	91.15 (17.15)	3.55 (0.81)	-0.86 [-3.08; 1.37]
Total							-1.28 [-2.81; 0.25][d]
Peripheral vision subscale							
RHINE	275	80.25 (23.99)	5.50 (1.01)	259	81.31 (23.30)	6.06 (1.04)	-0.56 [-3.41; 2.29]
YOSEMITE	256	75.40 (25.48)	7.11 (1.09)	246	80.86 (22.47)	6.04 (1.11)	1.07 [-1.99; 4.13]
Total							0.27 [-1.82; 2.35][d]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Unless otherwise indicated: MMRM with the covariables of treatment, visit, interaction between treatment and visit, and baseline value, adjusted for the stratification factor of randomization (BCVA at Day 1 [< 64 vs. ≥ 64 ETDRS letters]), prior treatment with intravitreal anti-VEGF therapies [yes vs. no], and region [USA/Canada vs. Asia/rest of the world]) for pooled analysis additionally stratified by study; effect relates to the difference in mean change at Week 52; observations after a COVID-19-related event were disregarded in the analysis.
c. Higher (increasing) values indicate better symptoms / health-related quality of life; favourable effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
d. Calculated from IPD metaanalysis with factor of study as a fixed effect (see footnote "b" on the model).
e. The percentage of participants included in the analysis is < 70%.

BCVA: best-corrected visual acuity; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ETDRS: Early Treatment Diabetic Retinopathy Study; IPD: individual patient data; MD: mean difference; MMRM: mixed model repeated measures; N: number of analysed patients; ND: no data; NEI VFQ-25: National Eye Institute Function Questionnaire-25; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; VEGF: vascular endothelial growth factor

Based on the available data, no more than proof, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

For the outcome of all-cause mortality, the metaanalysis of the RHINE and YOSEMITE studies does not show any statistically significant differences between treatment groups. This results in no hint of an added benefit of faricimab in comparison with aflibercept; an added benefit is therefore not proven.

Morbidity

BCVA

For the outcome of BCVA (responder analysis on improvement by ≥ 10 ETDRS letters), the metaanalysis of the RHINE and YOSEMITE studies showed no statistically significant differences between treatment groups. This results in no hint of an added benefit of faricimab in comparison with aflibercept; an added benefit is therefore not proven.

Health status (NEI VFQ-25, general health subscale)

For the outcome of health status (surveyed via NEI VFQ-25 general health subscale), the metaanalysis of the RHINE and YOSEMITE studies does not show any statistically significant differences between treatment groups. This results in no hint of an added benefit of faricimab in comparison with aflibercept; an added benefit is therefore not proven.

Health-related quality of life

NEI VFQ-25 (sum score)

For the outcome of health-related quality of life (surveyed via NEI VFQ-25 summary score), the metaanalysis of the RHINE and YOSEMITE studies does not show any statistically significant differences between treatment groups. This results in no hint of an added benefit of faricimab in comparison with aflibercept; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs, ocular AEs, and ocular SAEs

The metaanalysis of the RHINE and YOSEMITE studies showed no statistically significant differences between treatment groups for any of the outcomes of SAEs, discontinuation due to AEs, ocular AEs, or ocular SAEs. Hence, there is no hint of greater or lesser harm from faricimab in comparison with aflibercept for any of them; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account in the present assessment:

- age (< 65 years versus ≥ 65 years)

- sex (female versus male)
- BCVA at Day 1 (< 64 ETDRS letters vs. ≥ 64 ETDRS letters)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

For the outcomes of health status and health-related quality of life (NEI VFQ-25), the dossier contains only subgroup analyses for the responder analyses, but not for the continuous analyses.

Table 14 presents the subgroup results of faricimab in comparison with aflibercept.

Table 14: Subgroups (side effects) – RCT, direct comparison: faricimab versus aflibercept

Outcome Characteristic Study Subgroup	Faricimab N	Faricimab Patients with event n (%)	Aflibercept N	Aflibercept Patients with event n (%)	Faricimab vs. aflibercept RR [95% CI]	Faricimab vs. aflibercept p-value
Side effects						
Discontinuation due to AE						
BCVA at Day 1						
RHINE						
< 64 ETDRS letters	143	ND	ND	ND	ND	ND
≥ 64 ETDRS letters	174	ND	ND	ND	ND	ND
YOSEMITE						
< 64 ETDRS letters	138	ND	ND	ND	ND	ND
≥ 64 ETDRS letters	175	ND	ND	ND	ND	ND
Total					Interaction:	0.002[a]
< 64 ETDRS letters	281	8 (2.8)	284	0 (0)	NC	0.004[b]
≥ 64 ETDRS letters	349	4 (1.1)	341	6 (1.8)	0.65 [0.19; 2.29][b]	0.501[b]

a. Interaction test based on log-binomial regression.
b. IPD metaanalysis, log-binomial regression with the factor of study as a fixed effect; p-value: Cochran-Mantel-Haenszel test.

AE: adverse event; BCVA: best-corrected visual acuity; CI: confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; IPD: individual patient data; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; RR: relative risk

For the outcome of discontinuation due to AEs, the metaanalysis showed an effect modification by the characteristic of BCVA at Day 1. For patients with a BCVA score of < 64 ETDRS letters, a statistically significant difference was shown to the disadvantage of faricimab in comparison with aflibercept. For patients with a BCVA score ≥ 64 ETDRS letters, in contrast, there was no statistically significant difference between treatment groups.

Since on the outcome of discontinuation due to AEs, the dossier does not contain sufficient information which would allow classifying it as serious/severe, the outcome of discontinuation due to AEs is allocated to the outcome category non-serious/non-severe side effects. On the basis of the presented results, the extent of the effect in the subgroup with a BCVA of < 64 ETDS letters is no more than marginal. Consequently the results from this subgroup analysis are overall deemed irrelevant in the present constellation and are disregarded in the benefit assessment.

In accordance with the methods described in the benefit assessment, no relevant effect modification by age, sex, or BCVA was identified for other outcomes for which the dossier contains subgroup analyses.

Supplementary note on the appropriate comparator therapy

The aflibercept SPC [23] was revised in December 2022. Aflibercept treatment is initiated with 5 consecutive monthly injections, followed by 1 injection every 2 months. As per the revised SPC, the physician may subsequently, based on functional and/or morphological findings, either maintain the 2-month treatment interval or individualize it using a treat-and-extend dosing regimen with 2-week adjustments. As per the original SPC [14], flexibilization of the treatment interval was possible only after 12 months. The present benefit assessment is based on the original ACT.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 15).

Table 15: Extent of added benefit at outcome level: faricimab versus aflibercept

Outcome category **Outcome**	**Faricimab vs. aflibercept** **Event rate (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0–2.9% vs. 1.3–1.6%[c] RR: 0.99 [0.40; 2.47] p = 0.981	Lesser/added benefit not proven
Morbidity		
BCVA (improvement by ≥ 10 ETDRS letters)	52.7–58.3% vs. 54.1–57.6%[c] RR: 1.00 [0.91; 1.10] p = 0.916	Lesser/added benefit not proven
Health status (NEI VFQ-25, general health subscale)	3.44–4.64 vs. 4.80–6.52[c] MD: -1.65 [-3.88; 0.59] p = ND	Lesser/added benefit not proven
Health-related quality of life		
NEI VFQ-25 (summary score)	7.07–7.96 vs. 7.51–7.93[c] MD: -0.20 [-1.55; 1.16] p = ND	Lesser/added benefit not proven
Side effects		
SAEs	16.3–24.6% vs. 18.5–18.6%[c] RR: 1.10 [0.88; 1.38] p = 0.408	Greater/lesser harm not proven
Discontinuation due to AEs	1.3%–2.6% vs. 1.0%[c] RR: 1.98 [0.75; 5.24] p = 0.162	Greater/lesser harm not proven
Ocular AEs	33.5–36.4% vs. 33.1–34.7%[c] RR: 1.03 [0.89; 1.20] p = 0.696	Greater/lesser harm not proven
Ocular SAEs	2.8–2.9% vs. 0.6–1.9%[c] RR: 2.23 [0.97; 5.08] p = 0.051	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category and the outcome's scale level, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_l).
c. Minimum and maximum proportions of events or mean changes in each treatment arm in the included studies.

AE: adverse event; BCVA: best-corrected visual acuity; CI: confidence interval; CI_l: lower limit of the confidence interval; CI_u: upper limit of the confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; MD: mean difference; NC: not calculable; ND: no data; NEI VFQ-25: National Eye Institute Function Questionnaire-25; RR: relative risk; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 16: Favourable and unfavourable effects from the assessment of faricimab compared to aflibercept

Favourable effects	**Unfavourable effects**
–	–

Overall, neither favourable nor unfavourable effects were found for faricimab in comparison with aflibercept.

In summary, there is no hint of added benefit of faricimab versus aflibercept for adults with visual impairment due to DMO; an added benefit is therefore not proven.

Table 17 summarizes the results of the assessment of added benefit of faricimab in comparison with the ACT.

Table 17: Faricimab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Visual impairment due to DMO[b] in adults	Ranibizumab or **aflibercept**	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Patients with visual impairment due to DMO are assumed to have foveal involvement. The presence of clinically significant macular oedema according to the ETDRS criteria is assumed.

ACT: appropriate comparator therapy; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study; G-BA: Federal Joint Committee

The assessment described above deviates from that by the company, which derived proof of non-quantifiable added benefit on the basis of the longer treatment interval of faricimab.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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