Faricimab
(visual impairment due to macular oedema secondary to retinal vein occlusion)

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

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[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
BCVA	best corrected visual acuity
BRVO	branch retinal vein occlusion
CRVO	central retinal vein occlusion
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HVO	hemiretinal vein occlusion
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
RVO	retinal vein occlusion
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 27 August 2024.

Research question

The aim of this report was to assess the added benefit of faricimab in comparison with ranibizumab or aflibercept as appropriate comparator therapy (ACT) in adult patients with visual impairment due to macular oedema secondary to retinal vein occlusion (RVO), branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of faricimab

Research question	Therapeutic indication	ACT[a]
1	Adult patients with visual impairment due to macular oedema secondary to BRVO	Ranibizumab or **aflibercept**
2	Adult patients with visual impairment due to macular oedema secondary to CRVO[b]	Ranibizumab or **aflibercept**

a. Presented is the respective 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 according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Adult patients with visual impairment due to macular oedema secondary to HVO were assigned to patient population 2.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HVO: hemiretinal vein occlusion; BRVO: branch retinal vein occlusion; CRVO: central retinal vein occlusion

The company followed the G-BA's specification and chose 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 the derivation of added benefit.

Results

Concurring with the company, the check did not identify any relevant study which would allow a comparison of faricimab with aflibercept. In its dossier, however, the company presents the results of the studies BALATON and COMINO as supplementary information.

The studies BALATON and COMINO are completed double-blind, multicentre RCTs comparing faricimab and aflibercept. The BALATON study included adult patients with visual impairment due to macular oedema secondary to BRVO and the COMINO study included patients with visual impairment secondary to CRVO or hemiretinal vein occlusion (HVO).

In both studies, patients received an intravitreal injection of faricimab or aflibercept at monthly intervals up to and including Week 20 (6 injections in total). According to the recommendations of the Summary of Product Characteristics (SPC), treatment with faricimab or aflibercept should initially be performed every 4 weeks. This may require 3 or more consecutive monthly injections. Subsequently, the treatment should be adjusted individually depending on the disease activity in accordance with a treat-and-extend dosing regimen. In the BALATON and COMINO studies, however, individual adjustment of the dosing regimen was only possible in the second half of the study from Week 24, a period in which all patients received faricimab and sham injections. Accordingly, comparative data for a treat-and-extend dosing regimen are not available.

Based on the data on best-corrected visual acuity and central visual field thickness, it can be seen that a large proportion of patients in the studies BALATON and COMINO had stabilized after just 8 to 12 weeks. Accordingly, a relevant proportion of patients continued to be treated with an unchanged treatment regimen despite stable findings. This does not concur with the requirements of the SPC.

Concurring with the company's assessment, the studies BALATON and COMINO are therefore not suitable for the benefit assessment.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of faricimab in comparison with the ACT; an added benefit is therefore not proven.

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

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

[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].

Table 3: Faricimab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Adult patients with visual impairment due to macular oedema secondary to BRVO	Ranibizumab or **aflibercept**	Added benefit not proven
2	Treatment of adults with visual impairment due to macular oedema secondary to CRVOb	Ranibizumab or **aflibercept**	Added benefit not proven

a. Presented is the respective 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 according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Adult patients with visual impairment due to macular oedema secondary to HVO were assigned to patient population 2.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HVO: hemiretinal vein occlusion; BRVO: branch retinal vein occlusion; CRVO: central retinal vein occlusion

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 ACT in adult patients with visual impairment due to macular oedema following RVO, BRVO or CRVO.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of faricimab

Research question	Therapeutic indication	ACT[a]
1	Adult patients with visual impairment due to macular oedema secondary to BRVO	Ranibizumab or **aflibercept**
2	Adult patients with visual impairment due to macular oedema secondary to CRVO[b]	Ranibizumab or **aflibercept**

a. Presented is the respective 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 according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Adult patients with visual impairment due to macular oedema secondary to HVO were assigned to patient population 2.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HVO: hemiretinal vein occlusion; BRVO: branch retinal vein occlusion; CRVO: central retinal vein occlusion

The company followed the G-BA's specification and chose 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 the derivation of added benefit. This does not correspond to the company's inclusion criteria, which did not specify a minimum duration. This deviation has no consequences for the present benefit assessment, as there are no suitable data for the comparison of faricimab and aflibercept for any of the research questions specified by the G-BA, regardless of the study duration (see Chapter I 3). The following assessment is carried out jointly for both research questions specified by the G-BA.

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: 1 July 2024)
- bibliographical literature search on faricimab (last search on 1 July 2024)
- search in trial registries/trial results databases for studies on faricimab (last search on 1 July 2024)
- search on the G-BA website for faricimab (last search on 1 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on faricimab (last search on 10 September 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check did not identify any relevant study which would allow a comparison of faricimab with aflibercept. However, the company also presents the results of the studies BALATON [3] and COMINO [3] for both research questions presented. The company justified the exclusion of both studies with a treatment regimen for faricimab and aflibercept that deviated from the SPC specifications.

The company's approach is appropriate. This is explained below.

Studies BALATON and COMINO

The studies BALATON and COMINO have an identical study design and are described together below, unless otherwise stated. The studies BALATON and COMINO are completed double-blind, multicentre RCTs comparing faricimab and aflibercept. The BALATON study included adult patients with visual impairment due to macular oedema secondary to BRVO and the COMINO study included patients with visual impairment secondary to CRVO or HVO.

In the BALATON study, a total of 553 patients were randomly assigned in a 1:1 ratio to treatment with faricimab (N = 276) or aflibercept alfa (N = 277). In the COMINO study, a total of 729 patients were randomized in a 1:1 ratio either to the treatment arm with faricimab (N = 366) or with aflibercept (N = 363).

Both studies were divided into two treatment phases. In the first treatment phase, patients received an intravitreal injection with 6 mg faricimab or 2 mg aflibercept at monthly intervals up to and including Week 20 (6 injections in total). The primary analysis of treatment phase 1 was conducted at Week 24, followed by a non-active controlled treatment phase 2, in which all patients received 6 mg faricimab and - to blind the treatment intervals - sham injections at different individualized intervals until Week 68. The final study visit took place at Week 72.

In both studies, the primary outcome was the change in best corrected visual acuity (BCVA) at Week 24. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Lack of consideration of individualized treatment adjustment according to the SPC

According to the SPC, treatment with faricimab should initially take place every 4 weeks [4]. This may require 3 or more consecutive monthly injections. Subsequently, the treatment should be adjusted individually depending on the disease activity in accordance with a treat-and-extend dosing regimen. Based on the medical assessment of the patient's anatomic and/or visual findings, the dosing interval can be extended in steps of up to 4 weeks.

After the initial injection, treatment with aflibercept should be continued at monthly intervals in accordance with the SPC until maximum visual acuity is achieved and/or there are no more signs of disease activity [5]. 3 or more consecutive monthly injections may be necessary. Analogous to faricimab, the treatment interval can be gradually extended according to a treat-and-extend dosing regimen under maintenance of the functional and/or morphological findings.

According to the SPC mentioned above, treatment can be individually adjusted depending on the disease activity after 3 initial injections with faricimab or aflibercept. The joint comments of the Professional Association of German Ophthalmologists, the German Ophthalmological Society, and the Retinological Society on the intravitreal treatment of vision-impairing macular oedema in retinal vein occlusion [6] recommend an initial monitoring of the response after 3 monthly injections and a continuation with another 3 monthly injections if further treatment is required. Individual flexibilization of the treatment regimen is recommended from the 7th month of treatment. In the studies BALATON and COMINO, flexibilization of the treatment regimen was only carried out in the second study phase that was no longer comparative. Thus, there is no evidence on the comparison of faricimab and aflibercept using a treat-and-extend dosing regimen.

The European Public Assessment Report shows that the European Medicines Agency had also recommended a treat-and-extend dosing regimen in both arms as part of the consultation, but that this recommendation was not followed by the company [7].

In the BALATON study, the proportion of patients whose visual acuity had improved by ≥ 15 letters when analysing the BCVA at Week 24 was 53% in the faricimab arm and 55% in the aflibercept arm. In the COMINO study, 54% of the patients under faricimab and 55% under aflibercept had achieved an improvement in visual acuity by ≥ 15 letters by Week 24. Approx. 50% (BALATON study) and 53% (COMINO study) of patients already achieved this improvement by Week 12. In both studies, the average improvement in visual acuity of all patients was 17 letters at Week 24, and there was a plateau between Weeks 8 and 12.

Moreover, the analyses of the average central subfield thickness also show a plateau after approximately 8 to 12 weeks of treatment in both studies. It can therefore be assumed that in the studies BALATON and COMINO, the disease had stabilized in a large proportion of patients after just 8 to 12 weeks and that the treatment regimen could have been made individually more flexible.

Accordingly, a relevant proportion of patients continued to be treated with an unchanged treatment regimen despite stable findings. This does not concur with the requirements of the SPC.

Concurring with the company's assessment, the studies BALATON and COMINO are therefore not suitable for the benefit assessment.

I 4 Results on added benefit

No suitable data are available for the assessment of added benefit of faricimab in adult patients with visual impairment due to macular oedema following an RVO. For both research questions, there was no hint of added benefit of faricimab compared with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 presents a summary of the probability and extent of added benefit of faricimab.

Table 5: Faricimab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with visual impairment due to macular oedema secondary to BRVO	Ranibizumab or **aflibercept**	Added benefit not proven
2	Treatment of adults with visual impairment due to macular oedema secondary to CRVO[b]	Ranibizumab or **aflibercept**	Added benefit not proven

a. Presented is the respective 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 according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Adult patients with visual impairment due to macular oedema secondary to HVO were assigned to patient population 2.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HVO: hemiretinal vein occlusion; BRVO: branch retinal vein occlusion; CRVO: central retinal vein occlusion

The assessment described above concurs with that by the company.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Tadayoni R, Paris LP, Danzig CJ et al. Efficacy and Safety of Faricimab for Macular Edema due to Retinal Vein Occlusion: 24-Week Results from the BALATON and COMINO Trials. Ophthalmology 2024. https://doi.org/10.1016/j.ophtha.2024.01.029.

4. Roche. Vabysmo 120 mg/ml Injektionslösung [online]. 2024 [Accessed: 22.08.2024]. URL: https://www.fachinfo.de.

5. Bayer. Eylea 40 mg/ml Injektionslösung in einer Durchstechflasche [online]. 2023 [Accessed: 22.08.2024]. URL: https://www.fachinfo.de.

6. Deutsche Ophthalmologische Gesellschaft, Retinologische Gesellschaft, Berufsverband der Augenärzte Deutschlands. Stellungnahme von BVA, DOG und RG zur intravitrealen Therapie des visusmindernden Makulaödems bei retinalem Venenverschluss. Klinische Monatsblätter für Augenheilkunde 2018; 235(10): 1165-1177. https://doi.org/10.1055/a-0731-8952.

7. European Medicines Agency. Vabysmo: CHMP extension of indication variation assessment report [online]. 2024 [Accessed: 04.09.2024]. URL: https://www.ema.europa.eu/en/documents/variation-report/vabysmo-h-c-5642-ii-0005-epar-assessment-report-variation_en.pdf.

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