IQWiG Reports – Commission No. A20-23

Brolucizumab (neovascular age-related macular degeneration) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Brolucizumab (neovaskuläre altersabhängige Makuladegeneration) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 28 July 2020). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 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 brolucizumab. 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 10 March 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of this report is to assess the added benefit of brolucizumab in comparison with ranibizumab or aflibercept as the appropriate comparator therapy (ACT) in adult patients with neovascular (wet) age-related macular degeneration.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research questions of the benefit assessment of brolucizumab

Research question	Therapeutic indication	ACT[a]
1	Adult patients with neovascular (wet) age-related macular degeneration	Ranibizumab or aflibercept
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

Results

No studies relevant for the benefit assessment were found. The studies conducted by the company failed to implement the ACT of ranibizumab or aflibercept in accordance with the respective Summary of Product Characteristics (SPC). One potentially relevant study has not yet produced any results.

No data are available for the assessment of added benefit of brolucizumab in adult patients with neovascular (wet) age-related macular degeneration. Hence, there is no hint of added benefit of brolucizumab in comparison with ranibizumab or aflibercept. An added benefit is therefore not proven.

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

No data are available for the assessment of added benefit of brolucizumab in adult patients with neovascular (wet) age-related macular degeneration in comparison with the ACT. An added benefit of brolucizumab is therefore not proven.

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

Table 3: Brolucizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with neovascular (wet) age-related macular degeneration	Ranibizumab or aflibercept	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of brolucizumab in comparison with ranibizumab or aflibercept as the ACT in adult patients with neovascular (wet) age-related macular degeneration.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research questions of the benefit assessment of brolucizumab

Research question	Therapeutic indication	ACT[a]
1	Adult patients with neovascular (wet) age-related macular degeneration	Ranibizumab or aflibercept
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; 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 company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 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 brolucizumab (status: 02 January 2020)
- Bibliographic literature search on brolucizumab (most recent search on 02 January 2020)
- Search in trial registries for studies on brolucizumab (most recent search on 02 January 2020)
- Search on the G-BA website on brolucizumab (most recent search on 02 January 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on brolucizumab (most recent search on 16 March 2020)

The check did not identify any relevant studies.

Company's approach

In its information retrieval for the given research question, the company does not identify any relevant data.

In its dossier, the company names the following 5 RCTs, which it considers irrelevant: SEE (C-10-083) [3,4], OSPREY (C-12-006) [5,6], HAWK (RTH258-C001) [7,8], HARRIER (RTH258-C002) [8,9] and TALON (CRTH258A2303) [10]. All 5 RCTs are company-sponsored studies, and the studies SEE (C-10-083), OSPREY (C-12-006), HAWK (RTH258-C001), and HARRIER (RTH258-C002) are the approval studies for brolucizumab.

In the SEE study (C-10-083), brolucizumab was compared with ranibizumab, and in the OSPREY (C-12-006), HAWK (RTH258-C001), and HARRIER studies (RTH258-C002), it was compared with aflibercept. In the company's view, none of the studies administered the drugs aflibercept and ranibizumab in accordance with the respective SPC [11,12]; therefore, the company did not consider them further.

The TALON study (CRTH258A2303) likewise compares brolucizumab with aflibercept in adult patients with neovascular (wet) age-related macular degeneration (see Appendix A of the

full dossier assessment). However, the company did not include this study since no results are available yet.

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

Studies of the company failing to implement the ACT and potentially relevant studies without available results at this time

Studies of the company on the comparison of brolucizumab with ranibizumab

The SPC specifies that, after treatment initiation, ranibizumab is to be applied once per month. Monthly treatment is to be continued until maximum visual acuity is achieved and/or until there are no signs of disease activity. Thereafter, monitoring and treatment intervals should be determined by the physician based on visual acuity and/or morphological parameters.

In the SEE study (C-10-083) deviated from the SPC in that it administered only 1 injection of ranibizumab. According to the study plan, no further injections were planned. The individual adjustment specified in the SPC was omitted. Hence, the SEE study (C-10-083) did not implement the ACT.

Studies of the company on the comparison of brolucizumab with aflibercept

The SPC specifies that aflibercept therapy be initiated with 3 consecutive monthly injections. Thereafter, the treatment interval is to be extended to 2 months. Based on functional and/or morphological findings, the physician may maintain the treatment interval of once every 2 months or extend it further for the individual patient in 2-week or 4-week increments using a treat-and-extend dosing scheme (injection administered at every follow-up visit, with findings influencing the length of the next interval). In case of deterioration of functional and/or morphological findings, the treatment interval should be shortened within the first 12 months of treatment (by 2 or 4 weeks).

The OSPREY (C-12-006), HAWK (RTH258-C001), and HARRIER (RTH258-C002) studies deviated from the SPC in that, following treatment initiation with 3 monthly injections of aflibercept, the drug was applied at fixed 8-week intervals. Individualization of the treatment interval on the basis of functional and/or morphological findings, as specified in the SPC, was disregarded in these studies.

The ongoing, double-blind, multicentre RCT TALON (CRTH258A2303) compares brolucizumab with aflibercept in adults (≥ 50 years) with neovascular (wet), age-related macular degeneration who have not yet received any treatment against the vascular endothelial growth factor (VEGF) (see Appendix A of the full dossier assessment). The planned final total of 692 patients are to be randomly allocated to the treatment groups in a 1:1 ratio.

In this study, treatment with brolucizumab and aflibercept is initiated in accordance with the respective SPC, using 3 consecutive monthly injections. For both drugs, this is followed by another injection after 8 weeks and subsequent treat-to-control treatment from Week 16. The

treat-to-control phase permits an individualized adaptation of treatment intervals based on disease activity. However, the publicly available information does not show the extent to which the implementation of the treat-to-control dosing scheme in the TALON study corresponds to the brolucizumab or aflibercept SPC. Therefore, the extent to which the ACT is fully implemented in the TALON study cannot be assessed.

Outcomes investigated in the TALON study include mean change in best corrected visual acuity, distribution of examination or injection intervals without disease activity, as well as further outcomes on symptoms and health-related quality of life.

All things considered, the TALON study is potentially relevant for assessing the added benefit of brolucizumab in comparison with the ACT, provided that the treat-to-control scheme corresponds to the dosing scheme described in the respective SPCs. No results on this study are currently available, however, and the study is therefore not used in the present benefit assessment. According to the clinicaltrials.gov entry, initial results are expected by 20 May 2021 and final results by 04 March 2022.

Summary

No studies relevant for the present benefit assessment were found. The majority of the studies conducted by the company failed to implement the ACT of ranibizumab or aflibercept in accordance with the respective SPC. The potentially relevant TALON study has not yet produced any results.

2.4 Results on added benefit

No data are available for the assessment of added benefit of brolucizumab in adult patients with neovascular (wet) age-related macular degeneration. Hence, there is no hint of added benefit of brolucizumab in comparison with the ACT of ranibizumab or aflibercept. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

No data are available for the assessment of added benefit of brolucizumab in adult patients with neovascular (wet) age-related macular degeneration in comparison with the ACT. An added benefit of brolucizumab is therefore not proven.

Table 5 presents a summary of the results of the benefit assessment of brolucizumab in comparison with the ACT.

Table 5: Brolucizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with neovascular (wet) age-related macular degeneration	Ranibizumab or aflibercept	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The above assessment concurs with that of the company.

The G-BA decides on the added benefit.

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. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J 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.

3. Alcon Research. ESBA1008 safety, tolerability and effects in wet age-related macular degeneration (AMD) patients: study details [online]. In: ClinicalTrials.gov. 17.07.2014 [Accessed: 17.04.2020]. URL: https://ClinicalTrials.gov/show/NCT01304693.

4. Holz FG, Dugel PU, Weissgerber G, Hamilton R, Silva R, Bandello F et al. Single-chain antibody fragment VEGF inhibitor RTH258 for neovascular age-related macular degeneration: a randomized controlled study. Ophthalmology 2016; 123(5): 1080-1089.

5. Alcon Research. Efficacy and safety study of ESBA1008 versus EYLEA: study details [online]. In: ClinicalTrials.gov. 09.02.2016 [Accessed: 17.04.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT01796964.

6. Dugel PU, Jaffe GJ, Sallstig P, Warburton J, Weichselberger A, Wieland M et al. Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. Ophthalmology 2017; 124(9): 1296-1304.

7. Alcon Research. Efficacy and safety of RTH258 versus aflibercept: study 1 (HAWK); study details [online]. In: ClinicalTrials.gov. 13.01.2020 [Accessed: 17.04.2020]. URL: https://ClinicalTrials.gov/show/NCT02307682.

8. Dugel PU, Koh A, Ogura Y, Jaffe GJ, Schmidt-Erfurth U, Brown DM et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology 2020; 127(1): 72-84.

9. Alcon Research. Efficacy and safety of RTH258 versus aflibercept: study 2 (HARRIER); study details [online]. In: ClinicalTrials.gov. 31.10.2019 [Accessed: 17.04.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT02434328.

10. Novartis Pharmaceuticals. Study to assess the efficacy and safety of brolucizumab 6mg compared to aflibercept 2 mg in a treat-to-control regimen (TALON): study details [online]. In: ClinicalTrials.gov. 10.04.2020 [Accessed: 17.04.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04005352.

11. Bayer. Fachinformation Eylea 40 mg/ml Injektionslösung in einer Durchstechflasche [online]. 05.2019 [Accessed: 17.04.2020]. URL: http://www.fachinfo.de.

12. Pharma N. Fachinformation Lucentis Fertigspritze [online]. 10.2019 [Accessed: 17.04.2020]. URL: http://www.fachinfo.de.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a20-23-brolucizumab-neovascular-age-related-macular-degeneration-benefit-assessment-according-to-35a-social-code-book-v.13054.html.