Brolucizumab (neovascular age-related macular degeneration)

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

EXTRACT

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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
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

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has 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 20 October 2023.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. In this procedure, the G-BA limited its decision until 1 November 2023. The limitation was set due to the ongoing randomized controlled trial (RCT) TALON, for which no results were available at the time of the previous benefit assessment procedure. For the reassessment after expiry of the decision, the results of the TALON study on brolucizumab in comparison with the appropriate comparator therapy (ACT) have to be presented.

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

Table 2: Research question of the benefit assessment of brolucizumab

Therapeutic indication	**ACT**[a]
Adults with neovascular (wet) age-related macular degeneration	Ranibizumab or **aflibercept**
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification on 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 deviates from the company's inclusion criteria, which specified a minimum duration of 52 weeks.

Results

The check of the completeness of the study pool identified the RCT Talon on the direct comparison of brolucizumab with aflibercept. Although the company cited the RCT TALON, it

classified it as not relevant for the present benefit assessment. This assessment is inadequate on the basis of the available information.

Approach of the company

In its argumentation, the company only addresses the intervention arm and justifies the exclusion of the TALON study by stating that the dosing intervals and treatment regimens possible in the study do not correspond to the specifications of the currently valid Summary of Product Characteristics (SPC) for brolucizumab. Originally, according to the first version of the study protocol dated 5 April 2019, the minimum allowed dosing interval of brolucizumab and aflibercept in the maintenance phase was 4 weeks. Due to a safety measure, the study protocol of the TALON study and the SPC for brolucizumab were amended on 13 August 2021. The change was that the minimum dosing interval between 2 injections in the maintenance phase had to be at least 8 weeks. The change to the study protocol of the TALON study applied to both treatment arms. However, according to the current SPC, aflibercept may continue to be administered in a 4-week dosing interval in the maintenance phase.

Lack of information on the SPC-compliant use of the study medication

In Module 4 A, the company provides no data to support the statement that the patients in the intervention arm were not treated according to the current SPC for brolucizumab. The company's argumentation and the data available in Module 5 are not sufficient to comprehend the exclusion of the TALON study. Data are needed on how many patients in the brolucizumab arm actually received a dosing interval of less than 8 weeks in the maintenance phase and how long this lasted. Overall, however, based on the information in the study report, it cannot be assumed that the proportion of patients in the brolucizumab arm who were not treated in compliance with the SPC justifies an exclusion from the TALON study. For the aflibercept arm, based on the information in Module 5 (study report, study protocol and statistical analysis plan) of the TALON study, it can also be assumed that the data at Week 32 are relevant for the present benefit assessment. Under these assumptions, the exclusion of the TALON study is not appropriate.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of brolucizumab 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]

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

Table 3 summarizes 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**
Adults with neovascular (wet) age-related macular degeneration	Ranibizumab or **aflibercept**	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

[33] 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].

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

Table 4: Research question of the benefit assessment of brolucizumab

Therapeutic indication	**ACT**[a]
Adults with neovascular (wet) age-related macular degeneration	Ranibizumab or **aflibercept**
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification on 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 any added benefit. This deviates from the company’s inclusion criteria, which specified a minimum duration of 52 weeks.

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 brolucizumab (status: 01 September 2023)
- bibliographical literature search on brolucizumab (last search on 16 August 2023)
- search in trial registries/trial results databases for studies on brolucizumab (last search on 16 August 2023)
- search on the G-BA website for brolucizumab (last search on 17 August 2023)

To check the completeness of the study pool:

- search in trial registries for studies on brolucizumab (last search on 31 October 2023); for search strategies, see I Appendix A of the full dossier assessment

The check of the completeness of the study pool identified the RCT Talon on the direct comparison of brolucizumab with aflibercept. Although the company cited the RCT TALON, it classified it as not relevant for the present benefit assessment. This assessment is inadequate on the basis of the available information. This is justified below.

Approach of the company

In its information retrieval for the present research question, the company identified no relevant studies for the benefit assessment. Although it names the RCT TALON [3,4] in its dossier, which was classified as potentially relevant in the decision of the G-BA of 3 September 2020 [5] and is the basis of the limitation (see also Section I 2), it does not include it for the benefit assessment and does not prepare the data in the dossier.

The double-blind TALON study compared brolucizumab with aflibercept over a treatment period of 64 weeks and was terminated on 9 September 2022 (for further details on the TALON study, see 1st benefit assessment of brolucizumab A20-23 [6]). In its dossier, the company justifies the exclusion of the TALON study by stating that the dosing intervals and treatment regimens possible in the study do not correspond to the specifications of the currently valid SPC for brolucizumab [7]. Originally, according to the first version of the study protocol dated 5 April 2019, the minimum allowed dosing interval of brolucizumab and aflibercept in the maintenance phase was 4 weeks. Due to a safety measure, the study protocol of the TALON study and the SPC for brolucizumab were amended on 13 August 2021. The change was that the minimum dosing interval between 2 injections in the maintenance phase had to be at least 8 weeks. The change to the study protocol of the TALON study applied to both treatment

arms. However, according to the current SPC [8], aflibercept may continue to be administered in a 4-week dosing interval in the maintenance phase.

In addition to this change, a further revision of the SPC for brolucizumab resulted in the introduction of an additional, alternative treatment regimen for dose escalation, which was not possible in the TALON study.

In the company's view, brolucizumab was therefore not used in compliance with the current SPC in the TALON study [7] and no data were available from which the added benefit of brolucizumab versus the ACT could be derived.

Lack of information on the SPC-compliant use of the study medication

In Module 4 A, the company provides no information on how many patients in the two treatment arms were affected by the amendment of the study protocol of the TALON study described above and were therefore not treated in compliance with the respective SPC. In its argumentation, the company does not address the aflibercept arm, but refers exclusively to the brolucizumab arm.

The study report of the TALON study also contains no information on how many of the patients were not treated in compliance with the SPC for brolucizumab or aflibercept. However, the study report shows that over the entire study period of 64 weeks, a total of 16.4% (10.3% in the brolucizumab arm; 22.5% in the aflibercept arm) of patients had to discontinue the study treatment following a request from the sponsor ("sponsor request"). At Week 32, 9.0% of patients in the brolucizumab arm and 17.9% of patients in the aflibercept arm had to discontinue the study treatment at the request of the sponsor. The study report describes that the "sponsor request" primarily includes (see also below in the section "Further uncertainty") the patients who received a 4-week dosing interval in the maintenance phase or would have needed it after the study protocol amendment described above and therefore had to discontinue study treatment from the time of this study protocol amendment.

Brolucizumab arm

However, for the brolucizumab arm, it is overall unclear how many patients were not treated in compliance with the SPC. This is justified below:

- For one thing, it is unclear how many of the above-mentioned 10.3 % (at Week 64) or 9.0 % (at Week 32) of patients would have needed a 4-week dosing interval in the maintenance phase only after the change of the study protocol, which was no longer available now, e.g. due to the lack of treatment response and therefore had to discontinue study treatment immediately. These patients would have been treated in compliance with the current SPC for brolucizumab [7], as they never received a 4-week dosing interval in the maintenance phase.

- On the other hand, it is unclear whether patients received a 4-week dosing interval in the maintenance phase before the change of the study protocol, but had already been increased to a longer dosing interval at the time point of the study protocol amendment. These patients would not have been treated in compliance with the current SPC for brolucizumab [7], but would not be included in the above-mentioned 10.3% (at Week 64) or 9% (at Week 32) of patients who had to discontinue study treatment.

Overall, however, based on the information in the study report of the TALON study, it cannot be assumed that less than 80% of patients in the brolucizumab arm were not treated in compliance with the current SPC for brolucizumab [7] over the entire study period of 64 weeks or the period of 32 weeks. A proportion of at least 80 % of patients treated in compliance with the SPC is generally sufficient for the data to be used for the benefit assessment [1] . The company's argument for excluding the data is therefore not appropriate.

Aflibercept arm

According to the above-mentioned information in the study report, it can be assumed for the aflibercept arm that 22.5% of patients at Week 64 and 17.9% at Week 32 were not treated in compliance with the current SPC for Aflibercept [8]. These patients had to discontinue study treatment, although they could have been treated further at a 4-week dosing interval in the maintenance phase according to the current SPC for aflibercept [8]. Therefore, at Week 64, less than 80% of patients in the aflibercept arm would have been treated in compliance with the SPC. Exclusion of the data at Week 64 is therefore adequate for the benefit assessment. However, at Week 32, the proportion of patients in the aflibercept arm who were treated in compliance with the current SPC for Aflibercept was over 80%. Since an observation period of at least 24 weeks is sufficient in the therapeutic indication to be assessed, the data at Week 32 are suitable for the present benefit assessment.

Further uncertainty

As described above, the patients who had to discontinue study treatment in the TALON study due to a required 4-week dosing interval in the maintenance phase were listed under "Sponsor Request" in the study report. However, the rationale of the amendment that led to the described change in the study protocol also describes that patients with retinal vasculitis and/or retinal vascular occlusion also had to discontinue study treatment. It is therefore unclear whether the "Sponsor Request" category also includes patients who had to discontinue study treatment due to these mentioned events. If this is the case, the above-mentioned percentages of patients not treated in compliance with the SPC may be even lower in both treatment arms.

Summary

The company did not include the RCT Talon in its benefit assessment. In its argumentation, the company only addresses the intervention arm and justifies the exclusion of the TALON study by stating that the patients in the intervention arm had not been treated in compliance with the current SPC for brolucizumab. The company did not support this statement with data in Module 4 A . The company's argumentation and the data available in Module 5 are not sufficient to comprehend the exclusion of the TALON study. Data are needed on how many patients in the brolucizumab arm actually received a dosing interval of less than 8 weeks in the maintenance phase and how long this lasted. Overall, however, based on the information in the study report, it cannot be assumed that the proportion of patients in the brolucizumab arm who were not treated in compliance with the SPC justifies an exclusion from the TALON study. For the aflibercept arm, based on the information in Module 5 (study report, study protocol and statistical analysis plan) of the TALON study, it can be assumed that the data at Week 32 are relevant for the present benefit assessment. Under these assumptions, the exclusion of the TALON study is not appropriate.

I 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 was no hint of an added benefit of brolucizumab in comparison with the ACT ranibizumab or aflibercept. An added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

Table 5 summarizes the result of the assessment of the added benefit 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**
Adults with neovascular (wet) age-related macular degeneration	Ranibizumab or aflibercept	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above concurs with that of 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.

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