Bevacizumab gamma (neovascular age-related macular degeneration)

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

EXTRACT

Project: A25-57 Version: 1.0 Status: 29 Jul 2025 DOI: 10.60584/A25-57_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Bevacizumab (neovaskuläre altersbedingte Makuladegeneration) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Bevacizumab gamma (neovascular age-related macular degeneration) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

30 April 2025

Internal Project No.

A25-57

DOI-URL

https://doi.org/10.60584/A25-57_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Bevacizumab gamma (neovascular age-related macular degeneration); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-57_en.

Keywords

Bevacizumab, Macular Degeneration, Benefit Assessment

Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

No patients or families were involved in the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Ulrike Mikulić
- Tobias Effertz
- Lukas Gockel
- Mattea Patt
- Daniela Preukschat
- Veronika Schneck
- Dorothea Sow
- Corinna ten Thoren
- Yvonne Zens

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
CNV	choroidal neovascularisation
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)
SmPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book 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 bevacizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 30 April 2025.

Research question

The aim of this report is to assess the added benefit of bevacizumab gamma in comparison with the appropriate comparator therapy (ACT) in adult patients with neovascular (wet) age-related macular degeneration (AMD).

Bevacizumab gamma is the drug bevacizumab in an administration form adapted for ophthalmological use.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of bevacizumab gamma

Therapeutic indication	**ACT**[a, b]
Adult patients with neovascular (wet) age-related macular degeneration	Aflibercept or faricimab or **ranibizumab**

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 according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. The drugs of the specific ACT are suitable both for patients who are receiving treatment for their neovascular (wet) AMD for the first time and in the sense of a switch for patients previously treated with VEGF inhibitors after an insufficient response to the existing anti-VEGF therapy.

AMD: age-related macular degeneration; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

The company followed the G-BA's specification by choosing ranibizumab as 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) with a minimum duration of 24 weeks were used to derive the added benefit.

Results

Company dossier potentially incomplete in terms of content - potentially relevant studies with bevacizumab excluded without justification

The check of the completeness of the study pool identified 5 potentially relevant RCTs for a comparison of bevacizumab versus the option of the ACT ranibizumab selected by the company. These are the studies GEFAL, LUCAS, MANTA, CATT and IVAN. These are studies with intravitreal application of the drug avastin. Avastin is not approved for this therapeutic indication and is an intravenous administration form of bevacizumab according to the Summary of product characteristics (SmPC). The company also identified these studies, but excluded them without further justifying the exclusion and without addressing the possible transferability of the study results with avastin to the research question at hand. It merely states that only bevacizumab gamma was included as an intervention and that the trial registry entries were excluded with the exclusion reason "intervention (avastin)" in case of an off-label use of avastin. Whether further potentially relevant studies were excluded by the company as part of the bibliographic literature search due to this procedure was not checked.

The company's approach was not appropriate. Bevacizumab gamma was specially formulated for intravitreal application by adapting the pack size and buffer system. However, these adjustments do not per se argue against the use of studies with bevacizumab for the benefit assessment of bevacizumab gamma. The relevance of the 5 studies with bevacizumab was not conclusively verified. In principle, however, the 5 potentially relevant studies with bevacizumab are studies that (at least in subpopulations) enable an individualized dosage of bevacizumab or ranibizumab specified in the SmPC.

The pU dossier may be incomplete in terms of content due to the exclusion of studies involving bevacizumab (avastin).

The approach of the company with regard to the studies NORSE TWO and NORSE ONE is appropriate

In its information retrieval, the company identified no relevant data for the assessment of the added benefit of bevacizumab gamma. In its dossier, the company presents the results of the NORSE TWO study, supplemented by the results of the NORSE ONE study, as the best available evidence to describe the efficacy and tolerability of bevacizumab gamma. However, it does not use either study to assess the added benefit, citing the dosage of bevacizumab gamma in the studies as deviating from the approved dosage. The company's approach is appropriate, as in both studies, both in the intervention arm and in the comparator arm, the drugs were administered according to a fixed dosing regimen without allowing individual adjustment of the treatment interval according to the information provided in the SmPC.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of bevacizumab gamma 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 shows a summary of probability and extent of the added benefit of bevacizumab gamma.

Table 3. Bevacizumab gamma – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Adult patients with neovascular (wet) age-related macular degeneration	Aflibercept or faricimab or **ranibizumab**	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 according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. The drugs of the specific ACT are suitable both for patients who are receiving treatment for their neovascular (wet) AMD for the first time and in the sense of a switch for patients previously treated with VEGF inhibitors after an insufficient response to the existing anti-VEGF therapy.

AMD: age-related macular degeneration; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of this report is to assess the added benefit of bevacizumab gamma in comparison with the ACT in adult patients with neovascular (wet) AMD.

Bevacizumab gamma is the drug bevacizumab in an administration form adapted for ophthalmological use.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4. Research question of the benefit assessment of bevacizumab gamma

Therapeutic indication	**ACT**[a, b]
Adult patients with neovascular (wet) age-related macular degeneration	Aflibercept or faricimab or **ranibizumab**

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 according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. The drugs of the specific ACT are suitable both for patients who are receiving treatment for their neovascular (wet) AMD for the first time and in the sense of a switch for patients previously treated with VEGF inhibitors after an insufficient response to the existing anti-VEGF therapy.

AMD: age-related macular degeneration; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

The company followed the G-BA's specification by choosing ranibizumab as 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. RCTs with a minimum duration of 24 weeks were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on bevacizumab (status: 05 March 2025)
- Bibliographical literature search on bevacizumab (last search on 05 March 2025)
- Search in trial registries/trial results databases for studies on bevacizumab (last search on 06 March 2025)
- Search on the G-BA website for bevacizumab (last search on 05 March 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on bevacizumab (last search on 22 May 2025); for search strategies, see I Appendix A of the full dossier assessment

The company's searches are generally suitable for ensuring the completeness of the search results. However, in the selection, the company used the inappropriate exclusion criterion "intervention (avastin)" and thus excluded potentially relevant studies. This is described below.

Company dossier potentially incomplete in terms of content - potentially relevant studies with bevacizumab excluded without justification

The check of the completeness of the study pool identified 5 potentially relevant studies for a comparison of bevacizumab versus the option of the ACT ranibizumab selected by the company. These are the RCTs GEFAL [3], LUCAS [4], MANTA [5], CATT [6] and IVAN [7]. These are studies involving the intravitreal application of the drug avastin. Avastin is not approved for this therapeutic indication and is an intravenous administration form of bevacizumab according to the SmPC. The company also identified these studies, but excluded them without further justifying the exclusion and without addressing the possible transferability of the study results to the research question at hand. In a table in Appendix 4-D1 of Module 4 A, it merely states that only bevacizumab gamma was included as an intervention and that the trial registry entries with the exclusion reason "intervention (avastin)" were excluded in case of an off-label use of avastin [8]. Whether further potentially relevant studies were excluded by the company as part of the bibliographic literature search due to this procedure was not checked.

The company's approach was not appropriate. Bevacizumab gamma was specially formulated for intravitreal application by adapting the pack size and buffer system. However, these adjustments do not per se argue against the use of studies with bevacizumab for the benefit assessment of bevacizumab gamma. The relevance of the 5 studies with bevacizumab was not

conclusively verified. In principle, however, the 5 potentially relevant studies with bevacizumab are studies that (at least in subpopulations) enable individualized dosages of bevacizumab or ranibizumab specified in the SmPC. The company referred to the results of 2 of these studies (CATT and IVAN, both study arms with continuous administration) as supportive evidence in the approval procedure for bevacizumab gamma in the ophthalmological formulation to be assessed [9].

The pU dossier may be incomplete in terms of content due to the exclusion of studies involving bevacizumab (avastin).

The approach of the company with regard to the studies NORSE TWO and NORSE ONE is appropriate

In its information retrieval, the company identified no relevant data for the assessment of the added benefit of bevacizumab gamma. In its dossier, the company presents the results of the NORSE TWO study [10], supplemented by the results of the NORSE ONE study [11], as the best available evidence to describe the efficacy and tolerability of bevacizumab gamma. However, it does not use either study to assess the added benefit, citing the dosage of bevacizumab gamma in the studies as deviating from the approved dosage. The company's approach is appropriate. This is explained below.

Lack of consideration of individualized treatment adjustment

The NORSE TWO study is a double-blind, randomized phase III study in adult patients (≥ 50 years) with active primary subfoveal choroidal neovascularisation (CNV) secondary to AMD. A total of 228 patients were included and randomly assigned to the two study arms in a 1:1 ratio. In the intervention arm, patients received 1.25 mg bevacizumab gamma as a monthly intravitreal injection for up to 12 months. In the comparator arm, treatment consisted of 0.5 mg ranibizumab as a monthly intravitreal injection for 3 months, followed by 2 additional intravitreal injections on Days 150 and 240, as well as sham injections on the dates when ranibizumab administration was not scheduled. The primary outcome of the study was the proportion of study participants who achieved an improvement in visual acuity by ≥ 15 letters in the best corrected visual acuity (BCVA) score after 11 months compared to the baseline value. Further outcomes from the categories mortality, morbidity, and side effects were also recorded.

The NORSE ONE study is a double-blind, randomized phase III study in adult patients (≥ 50 years) with active primary or recurrent subfoveal CNV secondary to AMD. In contrast to the NORSE TWO study, anti-VEGF therapy before the start of the study was permitted. The allocation of a total of 61 patients to the two study arms was randomized in a 1:1 ratio. Treatment with bevacizumab gamma or ranibizumab corresponded to that in the NORSE TWO study. Primary outcome of the study was the proportion of study participants who achieved

an improvement in visual acuity by ≥ 15 letters in the BCVA score after 11 months compared to the baseline value. Further outcomes from the categories mortality, morbidity, and side effects were also recorded.

According to the SmPCs for bevacizumab gamma [12] and ranibizumab [13], treatment should be individualized. For bevacizumab gamma, treatment should be initiated with one injection per month and continued until maximum visual acuity is achieved and/or there are no signs of disease activity, i.e., no change in visual acuity or other signs and symptoms of the disease under continued treatment. This may require 3 or more consecutive monthly injections. The treatment interval should then be individually adjusted depending on the disease activity. If the patient does not benefit from continuing treatment, the drug should be discontinued [12]. Ranibizumab may also require 3 or more monthly injections until maximum visual acuity is achieved or there are no signs of disease activity. The initial monthly treatment interval should then be adjusted on the basis of the disease activity and interrupted if necessary. If patients are treated according to a treat-and-extend regimen, for example, the treatment interval can be extended individually by a maximum of two weeks per visit, depending on disease activity, until signs of disease activity or visual impairment return and a further shortening of the interval becomes necessary [13].

In the studies NORSE TWO and NORSE ONE, the drugs were administered in both study arms according to a fixed dosage regimen without allowing individual adjustment of the treatment interval. The failure to take into account the individual adjustment of treatment provided for in the SmPC in both the intervention arm and the comparator arm may have a relevant influence on the treatment result. According to the German Ophthalmological Society, the Retinological Society, and the Professional Association of German Ophthalmologists, consistent control examinations and optimization of individualized therapy according to the principle “as much as necessary, as little as possible” are crucial, with patient adherence being of key importance [14]. The studies NORSE TWO and NORSE ONE are therefore unsuitable for the benefit assessment.

Differences between the dosing regimens in the two study arms

In addition to the described deviations from the respective SmPC, the dosing regimens in the two study arms are also not comparable. While administration in the bevacizumab gamma arm took place monthly for the entire duration of the studies, ranibizumab was only administered monthly for the first 3 months. Thereafter, only 2 doses were administered, on Days 150 and 240. These differences between the dosing regimens potentially lead to an inequality between the two study arms.

Summary

The company's study selection is not appropriate due to the exclusion criterion "intervention (avastin)", which is not further justified, and the company's dossier is potentially incomplete in terms of content due to this. The relevance of the 5 studies identified as potentially relevant was not conclusively checked. However, in contrast to the company’s pivotal studies (NORSE ONE/TWO), these are basically studies that (at least in subpopulations) enable the individualization of the dosage of bevacizumab gamma or ranibizumab as specified in the SmPC.

The company's approach with regard to the studies NORSE ONE and NORSE TWO is appropriate. The studies are not suitable for the benefit assessment because of the failure to take into account the individualized adjustment of treatment provided for in the SmPC in the study design.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of bevacizumab gamma in adult patients with neovascular (wet) AMD. There was no hint of an added benefit of bevacizumab gamma in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of bevacizumab gamma in comparison with the ACT.

Table 5: Bevacizumab gamma – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b]	**Probability and extent of added benefit**
Adult patients with neovascular (wet) age-related macular degeneration	Aflibercept or faricimab or **ranibizumab**	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 according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b. The drugs of the specific ACT are suitable both for patients who are receiving treatment for their neovascular (wet) AMD for the first time and in the sense of a switch for patients previously treated with VEGF inhibitors after an insufficient response to the existing anti-VEGF therapy.

AMD: age-related macular degeneration; G-BA: Federal Joint Committee; VEGF: vascular endothelial growth factor

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: 02.09.2024]. 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. Hospices Civils de Lyon. French Evaluation Group Avastin Versus Lucentis (GEFAL) [online]. 2019 [Accessed: 04.06.2025]. URL: https://clinicaltrials.gov/study/NCT01170767.

4. Oslo University Hospital. LUCAS (Lucentis Compared to Avastin Study) (LUCAS) [online]. 2015 [Accessed: 04.06.2025]. URL: https://clinicaltrials.gov/study/NCT01127360.

5. Ludwig Boltzmann Institute of Retinology and Biomicroscopic Laser Surgery. Manta Study: Avastin Versus Lucentis in Age Related Macular Degeneration (MANTA) [online]. 2010 [Accessed: 04.06.2025]. URL: https://clinicaltrials.gov/study/NCT00710229.

6. University of Pennsylvania. Comparison of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial [online]. 2017 [Accessed: 04.06.2025]. URL: https://clinicaltrials.gov/study/NCT00593450.

7. Belfast Health and Social Care Trust, Queen's University Belfast, Research and Regional Services. A randomised control trial of alternative treatments to Inhibit VEGf in Age-related choroidal Neovascularisation(IVAN) [online]. [Accessed: 04.06.2025]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-001281-33.

8. Outlook Therapeutics. Bevacizumab gamma (Lytenava); Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 A. 2025: [Demnächst verfügbar unter: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1212/#dossier].

9. European Medicines Agency. Lytenava; Assessment report [online]. 2024 [Accessed: 25.06.2025]. URL: https://www.ema.europa.eu/en/documents/assessment-report/lytenava-epar-public-assessment-report_en.pdf.

10. Rahhal FM, Hu A, Humayun M et al. ONS-5010 (bevacizumab-vikg) Safety and Efficacy in Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration. Ophthalmic Surgery Lasers & Imaging Retina 2024. https://doi.org/10.3928/23258160-20240924-01.

11. Outlook Therapeutics. A Clinical Effectiveness Study Examining the Efficacy and Safety of ONS-5010 in Subjects With Neovascular Age-related Macular Degeneration (AMD) [online]. 2025 [Accessed: 04.06.2025]. URL: https://clinicaltrials.gov/study/NCT03844074.

12. Outlook Therapeutics. Fachinformation Lytenava 25 mg/ml Injektionslösung. 01.2025.

13. Novartis Pharma. Lucentis 10 mg/ml Injektionslösung [online]. 02.2023 [Accessed: 25.06.2025]. URL: https://www.fachinfo.de/.

14. Deutsche Ophthalmologische Gesellschaft, Retinologische Gesellschaft, Berufsverband der Augenärzte Deutschlands. Anti-VEGF-Therapie bei der neovaskulären altersabhängigen Makuladegeneration. Ophtalmologie 2023; 120(2): 169-177. https://doi.org/10.1007/s00347-022-01773-6.

The full report (German version) is published under
https://www.iqwig.de/en/projects/a25-57.html