IQWiG Reports – Commission No. A22-50

Brolucizumab (visual impairment due to diabetic macular oedema) –

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

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Brolucizumab (Visusbeeinträchtigung infolge eines diabetischen Makulaödems) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 July 2022). 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.

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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 two persons.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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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)
LOCF	last observation carried forward
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
OR	odds ratio
PT	Preferred Term
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VEGF	vascular endothelial growth factor

I 1 Benefit assessment

I 1.1 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 27 April 2022.

Research question

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

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

Table 2: Research question of the benefit assessment of brolucizumab

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 DME are assumed to have foveal involvement. The presence of a clinically significant macular oedema according to the ETDRS criteria is assumed. 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 the derivation of the added benefit.

Study pool and study design

The study pool for the benefit assessment of brolucizumab in comparison with aflibercept as ACT consisted of the studies KESTREL and KITE. Both studies are double-blind RCTs on the comparison of brolucizumab and aflibercept.

Both studies included adult patients with type 1 or type 2 diabetes mellitus and glycosylated haemoglobin (HbA1c) ≤ 10% at screening as well as visual impairment due to DMO. In each case, one eye was chosen as the study eye. The best corrected visual acuity (BCVA) of the study eye measured with Early Treatment Diabetic Retinopathy Study (ETDRS) vision charts had to

range between 78 and 23 ETDRS letters at a distance of 4 meters. Moreover, the DMO had to have foveal involvement and the retinal layer thickness had to be ≥ 320 µm.

The KESTREL study included a total of 566 patients, randomized in a 1:1:1 ratio either to treatment with brolucizumab 6 mg (N = 189) or brolucizumab 3 mg (N = 190) or aflibercept (N = 187). The brolucizumab arm with a dosage of 3 mg is not relevant for the present assessment, as the dosage did not correspond to the Summary of Product Characteristics (SPC). The KITE study included a total of 366 patients, randomized in a 1:1 ratio either to treatment with brolucizumab (N = 179) or aflibercept (N = 187).

In the intervention arm (6 mg) of the KESTREL study, patients received brolucizumab in accordance with the SPC. Deviating from this, an optional one-time prolongation of the treatment interval in the brolucizumab arm by 4 weeks was possible in the KITE study at week 72. In the comparator arms of the studies KESTREL and KITE, aflibercept was only administered until week 52, according to the SPC, as it was not possible to adjust the treatment interval after 1 year on the basis of functional and/or morphological findings.

Primary outcome in both studies was the change of BCVA at week 52 versus baseline. Patient-relevant outcomes on morbidity, health-related quality of life and side effects were additionally recorded in both studies.

Dates of analysis

The company's dossier provides data from an interim analysis at week 52 and from the final analysis at week 100 for both studies. In the present benefit assessment, the analyses at week 52 were used, as thereafter, aflibercept was no longer administered according to the SPC.

Risk of bias

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

The risk of bias of the results on the outcomes of all-cause mortality, serious adverse events (SAEs), discontinuation due to adverse events (AEs), intraocular inflammation (AEs) as well as intraocular inflammation (SAEs) was rated as low in both studies.

The risk of bias of the results on the outcome BCVA and on health-related quality of life (National Eye Institute Visual Functioning Questionnaire-25 [NEI VFQ-25]) was rated as high in both studies due to the high proportion of values that were imputed using last observation carried forward (LOCF) or categorized as non-responders.

Based on the available information, at most proofs, e.g. of added benefit, can be determined for the outcomes of all-cause mortality, SAEs, discontinuation due to AEs, intraocular inflammation (AEs) and intraocular inflammation (SAEs), and at most indications can be derived for the outcome of BCVA and health-related quality of life (NEI VFQ-25) due to the high risk of bias.

Results

Mortality

All-cause mortality

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of brolucizumab in comparison with aflibercept; an added benefit is therefore not proven.

Morbidity

BCVA

For the outcome “BCVA” (improvement by ≥ 10 ETDRS letters), the meta-analysis of the studies did not show any statistically significant differences between the treatment groups. This resulted in no hint of an added benefit of brolucizumab in comparison with aflibercept; an added benefit is therefore not proven.

Health-related quality of life

NEI VFQ-25

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the sum score of the NEI VFQ-25 (improvement by ≥ 15 points). This resulted in no hint of an added benefit of brolucizumab in comparison with aflibercept; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs, intraocular inflammation (AEs) and intraocular inflammation (SAEs)

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcomes "SAEs", "discontinuation due to AEs", “intraocular inflammation (AEs)” and “intraocular inflammation (SAEs)”. Consequently, there is no hint of greater or lesser harm from brolucizumab in comparison with aflibercept; greater or lesser harm is therefore not proven.

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

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

[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

The overall consideration shows neither positive nor negative effects for brolucizumab in comparison with aflibercept.

In summary, there is no hint of added benefit of brolucizumab versus aflibercept for adults with visual impairment due to DMO; an added benefit 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**
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 DME are assumed to have foveal involvement. The presence of a clinically significant macular oedema according to the ETDRS criteria is assumed.

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

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 1.2 Research question

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

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

Table 4: Research question of the benefit assessment of brolucizumab

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 DME are assumed to have foveal involvement. The presence of a clinically significant macular oedema according to the ETDRS criteria is assumed.

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

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 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 the derivation of the added benefit. This concurs with the company's inclusion criteria.

I 1.3 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: 17 February 2022)
- bibliographical literature search on brolucizumab (last search on 17 February 2022)
- search in trial registries/trial results databases for studies on brolucizumab (last search on 17 February 2022)
- search on the G-BA website for brolucizumab (last search on 17 February 2022)

To check the completeness of the study pool:

- search in trial registries for studies on brolucizumab (last search on 5 May 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 1.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: brolucizumab 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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
CRTH258B2301 (KESTREL[c])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7]
CRTH258B2302 (KITE[c])	Yes	Yes	No	Yes [8,9]	Yes [10-13]	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.
RCT: randomized controlled trial

The study pool for the benefit assessment of brolucizumab in comparison with aflibercept as ACT consists of the studies KESTREL and KITE and coincides with the company's study pool.

I 1.3.2 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: brolucizumab vs. aflibercept (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KESTREL	RCT, double-blind, parallel	Adult patients (≥ 18 years) with type 1 or type 2 diabetes mellitus (HbA1c ≤ 10% at screening) and visual impairment due to DMO[b]	▪ Brolucizumab 6 mg (N = 189) ▪ brolucizumab 3 mg (N = 190)[c] ▪ aflibercept 2 mg (N = 187)	▪ Screening: up to 2 weeks ▪ treatment: 96 weeks ▪ follow-up observation: 4 weeks	119 study centres in: Argentina, Australia, Austria, Canada, Columbia, Israel, Italy, Japan, Netherlands, Portugal, Spain, United Kingdom, USA 07/2018–10/2021 data cut-off: ▪ week 52: 11 November 2020 (interim analysis[d]) ▪ week 100: 18 October 2021 (final analysis after end of study)	▪ Primary: change in BCVA at week 52 vs. baseline ▪ secondary: mortality, morbidity, health-related quality of life, AEs
KITE	See KESTREL	See KESTREL	▪ Brolucizumab 6 mg (N = 179) ▪ aflibercept 2 mg (N = 181)	See KESTREL	79 study centres in: Belgium, Bulgaria, Czech Republic, Denmark, Estonia, France, Germany, Hungary, India, Korea Republic, Latvia, Lebanon, Lithuania, Malaysia, Norway, Poland, Russia, Singapore, Slovakia, Sweden, Switzerland, Taiwan, Turkey 07/2018–06/2021 data cut-off: ▪ week 52: 29 June 2020 (interim analysis[d]) ▪ week 100: 08 June 2021 (final analysis after end of study)	See KESTREL

Table 6: Characteristics of the studies included – RCT, direct comparison: brolucizumab vs. aflibercept (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

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
- BCVA between 78 and 23 ETDRS letters (each inclusive) using the ETDRS vision charts at a distance of 4 meters (corresponds approximately to a Snellen equivalent of 20/32 to 20/320) at screening and baseline.
- DMO with involvement of the fovea, with a retinal layer thickness (measured from the retinal pigment epithelium (RPE) to the inner limiting membrane (ILM), each inclusive) of ≥ 320 µm in spectral domain optical coherence tomography (SD-OCT) at screening.

If both eyes were suitable, the eye with the worse visual acuity was selected as the study eye. However, if medical or local ethical reasons prevented this, the investigator could also select the eye with the better visual acuity.

c. The arm is not relevant for the assessment and is not presented in the following tables.
d. The analysis of the data at week 52 represented the primary efficacy and safety analysis of the study. For this purpose, the database contains all data up to week 52 for all patients who completed the week 52 visit or discontinued the study prematurely. A second analysis was optionally planned after the blocking of the data of week 76 due to regulatory requirements, but was not carried out.

AE: adverse event; BCVA: best corrected visual acuity; DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study; HbA1c: glycosylated haemoglobin; ILM: inner limiting membrane; N: number of randomized patients; RCT: randomized controlled trial; RPE: retinal pigment epithelium; SD-OCT: spectral domain optical coherence tomography

Table 7: Characteristics of the intervention – RCT, direct comparison: brolucizumab vs. aflibercept (multipage table)

Study	Intervention	Comparison
KESTREL	Brolucizumab 6 mg/0.05 ml intravitreal operative injection of medication (IVOM) ▪ set-up phase: 5 times 1 injection every 6 weeks ▪ maintenance phase: 1 injection every 12 weeks or every 8 weeks[a] + sham injections according to aflibercept treatment regimen[c]	Aflibercept 2 mg/0.05 ml IVOM ▪ set-up phase: 5 times 1 injection every 4 weeks ▪ maintenance phase: 1 injection every 8 weeks[b] + sham injections according to brolucizumab treatment regimen[c]
	Dose adjustments ▪ dose adjustments and/or interruptions due to AEs were allowed **rescue treatment:** ▪ laser photocoagulation at disease activity possible in both treatment arms from week 36 onwards[d]	
	Prior and concomitant treatment ▪ stable diabetes medication within 3 months before randomization and in the further course of the study ▪ panretinal photocoagulation allowed at the investigator's discretion throughout the course of the study ▪ non-study eye: any standard treatments or other therapies for the treatment of an DMO and other diseases were allowed at any time **non-permitted concomitant treatment** study eye: ▪ intraocular or periocular corticosteroids (except short-term treatment of AEs) ▪ anti-VEGF therapy (except the study medication) ▪ focal/grid laser photocoagulation (before or at the time of the first identification of a disease activity) systemic: ▪ anti-VEGF therapy ▪ any investigational drug, biologic agent or procedure	
KITE	Brolucizumab 6 mg/0.05 ml IVOM ▪ set-up phase: 5 times 1 injection every 6 weeks ▪ maintenance phase: 1 injection every 12 weeks or every 8 weeks[a] (with optional treatment interval extended one-time by 4 weeks at week 72)[e] + sham injections according to aflibercept treatment regimen[c]	See KESTREL
	Dose adjustments and rescue treatment see KESTREL	
	Prior and concomitant treatment see KESTREL	

Table 7: Characteristics of the intervention – RCT, direct comparison: brolucizumab vs. aflibercept (multipage table)

Study	Intervention	Comparison
a. From week 36 onwards injections every 12 weeks, provided the investigator has not identified disease activity at week 32 (based on visual acuity and retinal, anatomic parameters); otherwise injections every 8 weeks from week 32 onwards. In case of disease activity in weeks 36, 48, 60, 72 or 84, the treatment interval was reduced to 8 weeks. b. An adjustment of the treatment interval was not possible in the aflibercept arm. c. To maintain masking, sham injections were administered in both treatment arms when active treatment was scheduled in the respective other arm. d. Criteria for rescue treatment: ▫ loss in visual acuity of ≥ 10 ETDRS letters in 2 consecutive visits due to DMO or ▫ loss in visual acuity of ≥ 15 ETDRS letters from the best previous measurement due to DMO and the patient's current BCVA score was not allowed to be better than the baseline score. Patients could receive laser photocoagulation and the assigned active study treatment during the same visit. Study treatment could be continued. e. At week 72, a one-time extension of the injection interval by 4 weeks was possible in the brolucizumab arm. BCVA: best corrected visual acuity; DMO: diabetic macular oedema; IVOM: intravitreal operative injection of medication; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor		

Study design

The studies KESTREL and KITE have a very similar study design and are described together below, unless otherwise stated. Both studies are double-blind RCTs on the comparison of brolucizumab and aflibercept.

Both studies included adult patients with type 1 or type 2 diabetes mellitus and HbA1c ≤ 10% at screening as well as visual impairment due to DMO. In each case, one eye was chosen as the study eye. The BCVA of the study eye measured with ETDRS vision charts had to range between 78 and 23 ETDRS letters at a distance of 4 meters. Moreover, the DMO had to have foveal involvement and the retinal layer thickness had to be ≥ 320 µm. If both eyes were suitable, the eye with the worse visual acuity was selected as the study eye. If medical or local ethical reasons prevented this, the investigator could also select the eye with the better visual acuity. However, it is not clear from the documents how many patients had both eyes meet the inclusion criteria of the studies and how many of them had the eye with the better visual acuity selected.

The KESTREL study included a total of 566 patients, randomized in a 1:1:1 ratio either to treatment with brolucizumab 6 mg (N = 189) or brolucizumab 3 mg (N = 190) or aflibercept (N = 187). The brolucizumab arm with a dosage of 3 mg is not relevant for the present assessment, as the dosage did not correspond to the SPC [14]. In the KESTREL study, randomization was stratified by family origin (Japanese vs. non-Japanese). The KITE study included a total of 366 patients, randomized in a 1:1 ratio either to treatment with brolucizumab (N = 179) or aflibercept (N = 187). Randomization in the KITE study was stratified by sampling for systemic exposure.

In the intervention arm (6 mg) of the KESTREL study, patients received brolucizumab in accordance with the SPC [14]. Deviating from this, an optional one-time prolongation of the treatment interval by 4 weeks was possible in the KITE study at week 72. In the comparator arms of the studies KESTREL and KITE, aflibercept was only administered until week 52, according to the SPC [15]. According to the SPC, the treatment interval could be extended after 1 year on the basis of functional and/or morphological findings according to a "treat and extend" dosing regimen or shortened accordingly in case of deterioration. However, adjustment of the treatment interval of aflibercept was impossible in both studies.

Primary outcome in both studies was the change of BCVA at week 52 versus baseline. Patient-relevant outcomes on morbidity, health-related quality of life and side effects were additionally recorded in both studies.

Dates of analysis

The company's dossier provides data from an interim analysis at week 52 and from the final analysis at week 100 for both studies. In the present benefit assessment, the analyses at week 52 were used in line with the approach of the company, as thereafter aflibercept was no longer administered according to the SPC (see above). Regardless of this, at week 100 there were neither positive nor negative effects for brolucizumab compared to aflibercept.

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations as well as discontinuation of the study/therapy – RCT, direct comparison: brolucizumab vs. aflibercept

Study characteristic category	KESTREL		KITE	
	brolucizumab	aflibercept	brolucizumab	aflibercept
	N[a] = 189	N[a] = 187	N[a] = 179	N[a] = 181
Age [years], mean (SD)	62 (10)	64 (10)	62 (11)	62 (9)
Sex [f/m], %	42/58	33/67	33/67	36/64
Family origin, (%)				
White	158 (84)	152 (81)	133 (74)	132 (73)
Black or African American	4 (2)	7 (4)	3 (2)	1 (1)
Asian	25 (13)	26 (14)	43 (24)	48 (27)
Other	2 (1)	2 (1)[b]	0 (0)	0 (0)
Type of diabetes, n (%)				
Type 1	12 (6)	6 (3)	19 (11)	7 (4)
Type 2	177 (94)	181 (97)	160 (89)	174 (96)
HbA1c [%], mean (SD)	7.7 (1.1)	7.4 (1.1)	7.5 (1.2)	7.5 (1.2)
Disease duration: time since DMO diagnosis [months], mean (SD)	9.4 (19.5)	9.6 (24.2)	10.4 (16.6)	9.9 (20.7)
BCVA [ETDRS letters], mean (SD)	66.6 (9.7)	65.2 (12.4)	66.0 (10.8)	63.7 (11.7)
BCVA category, n (%)				
< 60 ETDRS letters	36 (19)	41 (22)	42 (23)	50 (28)
≥ 60 ETDRS letters	153 (81)[b]	146 (78)[b]	137 (77)[b]	131 (72)[b]
Type of macular oedema, n (%)				
Focal	59 (31)	48 (26)	63 (35)	66 (36)
Diffuse	127 (67)	134 (72)	115 (64)	109 (60)
Missing value	3 (2)	5 (3)	1 (1)	6 (3)
Central Subfield Foveal Thickness (CSFT) [µm], MW (SD)	453.1 (123.4)	475.6 (135.8)	481.1 (132.5)	484.4 (134.6)
Treatment discontinuation, n (%)	25 (13.2)	18 (9.6)	19 (10.6)	15 (8.3)
Study discontinuation, n (%)	18 (9.5)	15 (8.0)	17 (9.5)	12 (6.6)

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.

BCVA: best corrected visual acuity; CSFT: Central Subfield Foveal 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 (or included) patients; RCT: randomized controlled trial; SD: standard deviation

Demographic characteristics are largely balanced between the 2 studies KESTREL and KITE as well as between their study arms. The majority of patients were of white family origin and on average over 60 years old. Less than half of the patients were female. The majority of patients had type 2 diabetes mellitus and a mean HbA1c of 7.4 to 7.7. The mean time since the DMO diagnosis was about 10 months and more than 70% of the patients had a BCVA of more than 60 ETDRS letters.

The proportion of patients with treatment discontinuation was about 10% in the treatment arms; the proportion of study discontinuations was < 10%.

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: brolucizumab versus aflibercept

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KESTREL	Yes	Yes	Yes	No	Yes	Yes	Low
KITE	Yes	Yes	Yes	No	Yes	Yes	Low
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

The company explained that brolucizumab and aflibercept were administered until week 52 in accordance with the SPC. Alternative treatment of the DMO would have been possible in case of treatment discontinuation, which would correspond to the recommendations of the German professional societies on the treatment of the DMO. The company said that, in terms of demographic and other characteristics, the patients in the studies were comparable to the patient population in Germany receiving anti-vascular endothelial growth factor (VEGF) therapy. Furthermore, according to the company, no statistically significant effects were found in the subgroup analyses according to the characteristic "region". Therefore, the company assumed transferability of the study results to the German health care context.

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

I 1.4 Results on added benefit

I 1.4.1 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-related quality of life
  - health-related quality of life (recorded using the NEI VFQ-25)
- Side effects
  - SAEs
  - discontinuation due to AEs
  - intraocular inflammation
  - intraocular inflammation (recorded with the company's prespecified PT list, 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 B).

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

Table 10: Matrix of outcomes – RCT, direct comparison: brolucizumab vs. aflibercept

Study	Outcomes							
	All-cause mortality	BCVA	Health-related quality of life (NEI VFQ-25)	SAEs	Discontinuation due to AEs	Intraocular inflammation[a] (AEs)	Intraocular inflammation[a] (SAEs)	Further specific AEs
KESTREL	Yes	Yes	Yes	Yes[b]	Yes[b]	Yes	Yes	No[c]
KITE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[c]

a. Recorded with the company's prespecified PT list; includes among others the PTs "iritis", "iridocyclitis", "uveitis", "eye inflammation", "retinal vasculitis" and "anterior chamber flicker".
b. Includes events of the underlying disease (PT "diabetic retinal oedema"); in the present data situation, however, the analyses were usable and suitable for the benefit assessment, as this event occurred only sporadically.
c. No further specific AEs were identified based on the AEs occurring in the relevant studies.

AE: adverse event; BCVA: best corrected visual acuity; NEI: National Eye Institute; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VFQ-25: Visual Functioning Questionnaire-25

Notes on outcomes

BCVA

In both studies, BCVA was measured using ETDRS vision charts [16,17]. The vision chart consists of 14 rows of vision signs with 5 letters each and is thus made up of a total of 70 letters. The size of the letters decreases with each row.

The vision test was performed at a distance of 4 meters from the ETDRS vision chart. If less than 20 letters could be read correctly from the vision chart, the distance was reduced to 1 meter. If neither at 4 nor at 1 meter distance at least 1 letter could be read correctly, further tests were scheduled if the respective previous test was not passed: recognition of the number of fingers shown, recognition of hand movements and light perception.

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 results directly from the number of correctly read letters. The BCVA can achieve values between 0 and 100, with higher values indicating better visual acuity.

The company presented analyses on both the improvement and the deterioration of the BCVA. Since according to the comments on the treatment of DMO [18] in the present therapeutic indication, treatment with intravitreal drugs such as brolucizumab or aflibercept should only take place if a positive influence on the findings can be expected, an analysis on the improvement of the BCVA is primarily relevant. According to the reasons described in the benefit assessments of ocriplasmin [19,20], the responder analysis on the improvement by ≥ 10 ETDRS letters (corresponds to 2 lines) was used for the present benefit assessment. The responder analysis on the improvement by ≥ 15 ETDRS letters (corresponds to 3 lines) is presented as supplementary information. According to the study protocol, patients who had a BCVA of ≥ 84 ETDRS letters in a survey after baseline were also considered responders in addition to patients with an increase in BCVA of ≥ 10 or ≥ 15 ETDRS letters. According to the company, this takes into account the ceiling effect that can occur with a relatively good initial function [18]. However, the company did not provide any information on how many patients were included in the analysis as responders on the basis of this criterion.

NEI VFQ-25

The NEI VFQ-25 is a questionnaire for measuring visus-related quality of life [21]. The questionnaire consists of a total of 26 items and 12 subscales, 25 items (11 subscales) of which are related to the visual acuity and 1 item (1 subscale) addresses general health. The sum score is calculated from the mean of the averaged scores of the subscales. In doing so, the item/subscale on general health is not included. The sum score can achieve values between 0 and 100, with higher values indicating better visus-related quality of life.

For the present benefit assessment, the responder analysis on the improvement of the sum score by ≥ 15 points is used because, as explained in the General Methods of the Institute [1], this reflects with sufficient certainty a patient-noticeable change. For the subscales, the company submitted only continuous analyses. In these analyses on the subscales (as in the sum score of the responder analysis), there is no statistically significant and relevant difference between the treatment arms.

I 1.4.2 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: brolucizumab versus aflibercept:

Study	Study level	Outcomes							
		All-cause mortality	BCVA	Health-related quality of life (NEI VFQ-25)	SAEs	Discontinuation due to AEs	Intraocular inflammation[a] (AEs)	Intraocular inflammation[a] (SAEs)	Further specific AEs
KESTREL	L	L	H[b]	H[b]	L	L	L	L	–
KITE	L	L	H[b]	H[b]	L	L	L	L	–

a. Recorded with the company's prespecified PT list; includes among others the PTs "iritis", "iridocyclitis", "uveitis", "eye inflammation", "retinal vasculitis" and "anterior chamber flicker".
b. High proportion of missing values, which were imputed with the last observation carried forward (LOCF) strategy or categorized as non-responders.

AE: adverse event; BCVA: best corrected visual acuity; H: high; LOCF: last observation carried forward; L: low; NEI: National Eye Institute; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VFQ-25: Visual Functioning Questionnaire-25

The risk of bias for the results on the outcomes of all-cause mortality and for all outcomes of the category of side effects was rated as low in both studies.

The risk of bias of the results on the outcome BCVA and on health-related quality of life (NEI VFQ-25) was rated as high in both studies due to the high proportion of values that were imputed using LOCF or categorized as non-responders.

I 1.4.3 Results

Table 12 summarizes the results on the comparison of brolucizumab with 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.

The company calculated the test for heterogeneity between the studies KESTREL and KITE using the effect measure "odds ratio (OR)". Therefore, separate tests for heterogeneity based on the effect measure "relative risk (RR)" were calculated for the outcomes of all-cause mortality, BCVA (improvement by ≥ 10 or ≥ 15 ETDRS letters), NEI VFQ-25 (sum score, improvement by ≥ 15 points), SAEs and discontinuation due to AEs as well as for the corresponding subgroup analyses.

The forest plots of the meta-analyses calculated by the Institute can be found in Appendix B of the full dossier assessment. Tables on common AEs, SAEs and discontinuation due to AEs are presented in Appendix C of the full dossier assessment.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brolucizumab vs. aflibercept (multipage table)

Time point outcome category outcome study	Brolucizumab		Aflibercept		Brolucizumab vs. aflibercept
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
Week 52					
Mortality					
All-cause mortality					
KESTREL	189	5 (2.6)	187	2 (1.1)	2.47 [0.49; 12.59]; 0.275
KITE	179	3 (1.7)	181	2 (1.1)	1.52 [0.26; 8.97]; 0.646
Total[a]					2.00 [0.61; 6.58]; 0.255
Morbidity					
BCVA (improvement by ≥ 10 ETDRS letters[b])					
KESTREL	189	99 (52.4)	187	107 (57.2)	0.92 [0.76; 1.10]; 0.347
KITE	179	110 (61.5)	181	106 (58.6)	1.05 [0.89; 1.24]; 0.576
Total[a]					0.98 [0.87; 1.11]; 0.771
BCVA (improvement by ≥ 15 ETDRS letters[b]), provided as supplementary information					
KESTREL	*189*	*70 (37.0)*	*187*	*74 (39.6)*	*0.94 [0.72; 1.21]; 0.613*
KITE	*179*	*83 (46.4)*	*181*	*68 (37.6)*	*1.23 [0.97; 1.58]; 0.092*
Total					*1.08 [0.90; 1.29]; 0.405*
Health-related quality of life					
NEI VFQ-25[c] (sum score, improvement by ≥ 15 points[d])					
KESTREL	188	46 (24.5)	187	43 (23.0)	1.06 [0.74; 1.53]; 0.737
KITE	178	37 (20.8)	181	33 (18.2)	1.14 [0.75; 1.74]; 0.542
Total[a]					1.10 [0.83; 1.44]; 0.510
Side effects[e]					
AEs (supplementary information)					
KESTREL	189	155 (82.0)	187	148 (79.1)	–
KITE	179	136 (76.0)	181	146 (80.7)	–
SAEs					
KESTREL	189	37 (19.6)	187	43 (23.0)	0.85 [0.58; 1.26]; 0.419
KITE	179	34 (19.0)	181	40 (22.1)	0.86 [0.57; 1.29]; 0.467
Total[a]					0.86 [0.65; 1.13]; 0.277
Discontinuation due to AEs					
KESTREL	189	4 (2.1)	187	7 (3.7)	0.57 [0.17; 1.90]; 0.356
KITE	179	10 (5.6)	181	8 (4.4)	1.26 [0.51; 3.13]; 0.612
Total[a]					0.94 [0.46; 1.91]; 0.856
Intraocular inflammation[f, g] (AEs)					
KESTREL	189	7 (3.7)	187	1 (0.5)	6.93 [0.86; 55.74]; 0.069
KITE	179	4 (2.2)	181	3 (1.7)	1.35 [0.31; 5.94]; 0.693

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brolucizumab vs. aflibercept (multipage table)

Time point outcome category outcome study	Brolucizumab		Aflibercept		Brolucizumab vs. aflibercept
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
Total[a]					2.75 [0.88; 8.60]; 0.081
Intraocular inflammation[f,h] (SAEs)					
KESTREL	189	0 (0.0)	187	0 (0.0)	NA
KITE	179	1 (0.6)	181	1 (0.6)	1.01 [0.06; 16.04]; 0.994
Total[a]					1.01 [0.06; 16.04]; 0.994

a. Institute's calculation, meta-analysis with fixed effect model according to Mantel-Haenzsel; test for homogeneity based on the effect measure "RR".
b. Proportion of patients with an increase in BCVA by ≥ 10 ETDRS letters (or by ≥ 15 ETDRS letters, presented as supplementary information) at week 52 compared to baseline, given a scale range of 0 to 100. Higher (increasing) values indicate an improvement of symptoms.
c. For the subscales, the company submitted only continuous analyses. These also show no statistically significant and relevant difference between the treatment arms.
d. Proportion of patients with an increase in the NEI VFQ-25 sum score by ≥ 15 points (≥ 15% of the scale range) at week 52 compared to baseline, given a scale range of 0 to 100. Higher (increasing) values indicate an improvement in health-related quality of life.
e. Includes events of the underlying disease (PT "diabetic retinal oedema"); however, the analysis was suitable for the benefit assessment, as this event occurred only sporadically.
f. Recorded with the company's prespecified PT list.
g. The PTs "iritis", "uveitis", "eye inflammation" and "retinal vasculitis" occurred in the KESTREL study; PTs that occurred in the KITE study were iridocyclitis, uveitis and anterior chamber flicker.
h. No event occurred in the KESTREL study, the PT "uveitis" occurred in the KITE study.

AE: adverse event; BCVA: best corrected visual acuity; CI: confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; n: number of patients with (at least one) event; N: number of analysed patients; NEI: National Eye Institute; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VFQ-25: Visual Functioning Questionnaire-25

Based on the available information, at most proofs, e.g. of added benefit, can be determined for the outcomes of all-cause mortality as well as for all outcomes of the category of side effects and at most indications can be derived for the outcomes of BCVA and health-related quality of life (NEI VFQ-25) due to the high risk of bias.

Mortality

All-cause mortality

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of brolucizumab in comparison with aflibercept; an added benefit is therefore not proven.

Morbidity

BCVA

For the outcome "BCVA" (improvement by ≥ 10 ETDRS letters), the meta-analysis of the studies did not show any statistically significant differences between the treatment groups. This resulted in no hint of an added benefit of brolucizumab in comparison with aflibercept; an added benefit is therefore not proven.

Health-related quality of life

NEI VFQ-25

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the sum score of the NEI VFQ-25 (improvement by ≥ 15 points). This resulted in no hint of an added benefit of brolucizumab in comparison with aflibercept; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs, intraocular inflammation (AEs) and intraocular inflammation (SAEs)

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcomes "SAEs", "discontinuation due to AEs", "intraocular inflammation (AEs)" and "intraocular inflammation (SAEs)". Consequently, there is no hint of greater or lesser harm from brolucizumab in comparison with aflibercept; greater or lesser harm is therefore not proven.

I 1.4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (female versus male)
- BCVA (≤ 65 ETDRS letters vs. > 65 ETDRS letters)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Only results showing 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 one subgroup.

For the outcomes used in the present benefit assessment, no relevant effect modification by age, sex or BCVA was identified in accordance with the methods described.

I 1.5 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 [22].

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 1.5.1 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 2.4 (see Table 13).

Table 13: Extent of added benefit at outcome level: brolucizumab versus aflibercept

Outcome category **outcome**	**Brolucizumab vs. aflibercept** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	2.6% and 1.7% vs. 1.1% RR: 2.00 [0.61; 6.58] p = 0.255	Lesser/added benefit not proven
Morbidity		
BCVA (improvement by ≥ 10 ETDRS letters)	52.4% and 61.5% vs. 57.2% and 58.6% RR: 0.98 [0.87; 1.11] p = 0.771	Lesser/added benefit not proven
Health-related quality of life		
NEI VFQ-25 (sum score, improvement by ≥ 15 points)	24.5% and 20.8% vs. 23.0% and 18.2% RR: 1.10 [0.83; 1.44] p = 0.510	Lesser/added benefit not proven
Side effects		
SAEs	19.6% and 19.0% vs. 23.0% and 22.1% RR: 0.86 [0.65; 1.13] p = 0.277	Greater/lesser harm not proven
Discontinuation due to AEs	2.1% and 5.6% vs. 3.7% and 4.4% RR: 0.94 [0.46; 1.91] p = 0.856	Greater/lesser harm not proven
Intraocular inflammation (AEs)	3.7% and 2.2% vs. 0.5% and 1.7% RR: 2.75 [0.88; 8.60] p = 0.081	Greater/lesser harm not proven
Intraocular inflammation (SAEs)	0% and 0.6% vs. 0% and 0.6% RR: 1.01 [0.06; 16.04] p = 0.994	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).

AE: adverse event; BCVA: best corrected visual acuity; CI: confidence interval; CI_u: upper limit of the confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; NEI: National Eye Institute; RR: relative risk; SAE: serious adverse event; VFQ-25: Visual Functioning Questionnaire-25

I 1.5.2 Overall conclusion on added benefit

Table 14 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of brolucizumab compared to aflibercept

Positive effects	**Negative effects**
–	–

The overall consideration shows neither positive nor negative effects for brolucizumab in comparison with aflibercept.

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

Table 15 summarizes the result of the assessment of the added benefit of brolucizumab in comparison with the ACT.

Table 15: Brolucizumab – 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 DME are assumed to have foveal involvement. The presence of a clinically significant macular oedema according to the ETDRS criteria is assumed. DMO: diabetic macular oedema; ETDRS: Early Treatment Diabetic Retinopathy Study; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived proof of a minor added benefit on the basis of the System Organ Class (SOC) “renal and urinary disorders”. However, the extent of the effect in this non-serious/non-severe outcome was no more than marginal.

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.

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 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.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://dx.doi.org/10.1002/bimj.201300274.

3. Novartis. A two-year, three-arm, randomized, double masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KESTREL); study CRTH258B2301; Clinical Study Report (Week 52 analysis) [unpublished]. 2021.

4. Novartis. A two-year, three-arm, randomized, double masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KESTREL); study CRTH258B2301; Clinical Study Report (Week 100 analysis) [unpublished]. 2022.

5. Novartis Pharma. A Two-Year, Three-Arm, Randomized, Double Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Diabetic Macular Edema (KESTREL) [online]. 2018 [Accessed: 25.05.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-004742-23.

6. Novartis Pharmaceuticals. Study of Efficacy and Safety of Brolucizumab vs. Aflibercept in Patients With Visual Impairment Due to Diabetic Macular Edema (KESTREL) [online]. 2022 [Accessed: 25.05.2022]. URL: https://ClinicalTrials.gov/show/NCT03481634.

7. Brown DM, Emanuelli A, Bandello F et al. KESTREL and KITE: 52-week results from two Phase III pivotal trials of brolucizumab for diabetic macular edema. Am J Ophthalmol 2022. https://dx.doi.org/10.1016/j.ajo.2022.01.004.

8. Novartis. A two-year, two-arm, randomized, double masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KITE); study CRTH258B2302; Clinical Study Report (Week 52 analysis) [unpublished]. 2021.

9. Novartis. A two-year, two-arm, randomized, double masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KITE); study CRTH258B2302; Clinical Study Report (Week 100 analysis) [unpublished]. 2022.

10. Novartis Healthcare. A Two-Year, Two-Arm, Randomized, Double-Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Diabetic Macular Edema - KITE [online]. 2022 [Accessed: 25.05.2022]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=26613".

11. Novartis Pharma. A Two-Year, Two-Arm, Randomized, Double Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Diabetic Macular Edema (KITE) [online]. 2018 [Accessed: 25.05.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-003960-11.

12. Novartis Pharma. A Two-Year, Two-Arm, Randomized, Double Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab Versus Aflibercept in Adult Patients With Visual Impairment Due to Diabetic Macular Edema [online]. 2018 [Accessed: 25.05.2022]. URL: https://lbctr.moph.gov.lb/Trials/Details/4886.

13. Novartis Pharmaceuticals. A Study of the Efficacy and Safety of Brolucizumab vs. Aflibercept in Patients With Visual Impairment Due to Diabetic Macular Edema (KITE) [online]. 2022 [Accessed: 25.05.2022]. URL: https://ClinicalTrials.gov/show/NCT03481660.

14. Novartis Europharm Limited. Fachinformation (Zusammenfassung der Merkmale des Arzneimittels/SmPC) Beovu Injektionslösung in einer Fertigspritze. Beovu Injektionslösung. Stand: März 2022. 2022.

15. Bayer AG. Fachinformation Eylea 40 mg/ml Injektionslösung in einer Fertigspritze. Stand: Juli 2021. 2021.

16. Ferris FL, Bailey I. Standardizing the Measurement of Visual Acuity for Clinical Research Studies: Guidelines from the Eye Care Technology Forum. Ophthalmology 1996; 103(1): 181-182. https://dx.doi.org/10.1016/S0161-6420(96)30742-2.

17. Ferris FL 3rd, Kassoff A, Bresnick GH et al. New visual acuity charts for clinical research. Am J Ophthalmol 1982; 94(1): 91-96.

18. Deutsche Ophthalmologische Gesellschaft, Retinologische Gesellschaft e V, Berufsverband der Augenarzte Deutschlands e V. [Statement of the German Ophthalmological Society, the Retinological Society and the Professional Association of Ophthalmologists in Germany on treatment of diabetic macular edema : Situation August 2019]. Ophthalmologe 2020; 117(3): 218-247. https://dx.doi.org/10.1007/s00347-019-01015-2.

19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ocriplasmin (vitreomakuläre Traktion): Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung [online]. 2019 [Accessed: 11.04.2019]. URL: https://www.iqwig.de/download/A18-68_Ocriplasmin_Nutzenbewertung-35a-SGB-V_V1-1.pdf.

20. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ocriplasmin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-20 [online]. 2013 [Accessed: 02.08.2013]. URL: https://www.iqwig.de/download/A13-20_Ocriplasmin_Nutzenbewertung-35a-SGB-V.pdf.

21. Mangione CM, Lee PP, Gutierrez PR et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001; 119(7): 1050-1058. https://dx.doi.org/10.1001/archopht.119.7.1050.

22. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a22-50.html.