Brolucizumab (neovascular age-related macular degeneration 1)

Addendum to Project A23-101 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
BCVA	best corrected visual acuity
ETDRS	Early Treatment Diabetic Retinopathy Study
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	neovascular age-related macular degeneration
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

1 Background

On 18 March 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-101 (Brolucizumab – Benefit assessment according to § 35a Social Code Book V) [1].

In its comments [2] and following the oral hearing, the pharmaceutical company (hereinafter referred to as “the company”) presented additional data that go beyond the information in the dossier. The commission comprised the assessment of the data presented by the company following the oral hearing [3Novartis Pharma, #33], taking into account the information in the dossier [4].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The company identified no relevant randomized controlled trial (RCT) for the benefit assessment of brolucizumab in comparison with ranibizumab or aflibercept as appropriate comparator therapy (ACT) in adult patients with neovascular (wet) age-related macular degeneration (nAMD). In Module 4 A [4], the company named the TALON study, but did not include it in the benefit assessment. 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 Summary of Product Characteristics (SPC) for brolucizumab [5]. However, the company did not support this statement with data in Module 4 A. The company's argumentation and the data available in Modules 4 and 5 were not sufficient to comprehend the exclusion of the TALON study. Among other things, data were needed on how many patients in the brolucizumab arm actually received a dosing interval of less than 8 weeks in the maintenance phase (i.e. the no longer permitted 4-week interval) and how long this lasted. However, based on the information in Module 5 (clinical study report, study protocol and statistical analysis plan [6]) of the TALON study, it can be assumed that the data at Week 32 are relevant for the present benefit assessment.

In the commenting procedure and following the oral hearing [2,3], the company subsequently submitted further data on the dosing intervals under 8 weeks in the brolucizumab arm. Moreover, the company presented analyses on outcomes of the categories of morbidity and side effects.

In the following, the data and analyses subsequently submitted by the company are assessed as commissioned.

2.1 Study characteristics

A detailed description of the TALON study can be found in dossier assessment A20-23 and A23-101 101 [1,7].

Relevance of the TALON study for the benefit assessment

Assessment of the SPC-compliant administration of brolucizumab until Week 32

In its comments [2], the company states that up to Week 32, a total of 80 patients (22%) from the brolucizumab arm had been treated at least once in the maintenance phase at an interval of less than 8 weeks and thus not in accordance with the current SPC of brolucizumab [5]. In its comments, the company further argued that the alternative up-titration described in the current SPC of brolucizumab was not possible in the TALON study and that this deviation from the SPC sufficiently justifies that the TALON study is not suitable for the benefit assessment. This reasoning of the company is not appropriate. This is justified below.

Dosing intervals of brolucizumab under 8 weeks (maintenance phase)

The data subsequently submitted by the company after the oral hearing [3] show that half of the 22% of patients mentioned above (11% in relation to the entire brolucizumab arm), had only one dosing interval of less than 8 weeks (in the maintenance phase). In addition, the company also includes those patients in these percentages who only deviated from an 8-week dosing interval by a few days during the maintenance phase (for example, there were 55 days instead of 56 days between two doses). However, the company's data provide no information on how many patients had undercut an 8-week dosing interval by only a few days in the maintenance phase. Although the company states the mean and median number of days between two injections for these 22% of patients, it is not clear whether these mean and median values also include the SPC-compliant 4-week up-titration intervals (see Table 1). Irrespective of this, the present benefit assessment considers a one-time shortfall of an eight-week dosing interval in the maintenance phase and, in particular, deviations of only a few days as a sufficient approximation to the SPC-compliant use of brolucizumab. The remaining uncertainty regarding the influence of a (pronounced) shortfall in the dosing interval on the results is taken into account in the reliability of the results (see Section 2.2.2).

Table 1: Additional information on brolucizumab dosing intervals (until Week 32)

Study characteristic category	**Brolucizumab N[a] = 366**
TALON (Week 32)	
Number of treatment intervals < 8 weeks in the maintenance phase, n (%)	
0	286 (78)
1	40 (11)
2	27 (7)
3	7 (2)
4	6 (2)
Duration between two injections [days][b]	N = 80
Median [min; max][c]	32.5 [23; 55]

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. In patients with at least one treatment interval < 8 in the maintenance phase.
c. The company's documents provide no information on whether the SPC-compliant up-titration at 4-week intervals within the first 3 doses is considered in the calculation of the period between two injections.

max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial

Alternative up-titration of brolucizumab

For the up-titration, the SPC of brolucizumab recommends a brolucizumab dose of 6 mg every 4 weeks for the first three doses. This up-titration was implemented in the TALON study. Alternatively, 6 mg brolucizumab can also be administered every 6 weeks for the first 2 doses according to the current SPC [5]. This alternative up-titration was not possible in the TALON study. However, the SPC does not provide any information or criteria according to which one of the two possible up-titrations should be preferred or selected on an individualized basis for the patients to be treated. It can therefore be assumed that both variants are equivalent. It is therefore not appropriate to exclude the TALON study due to the impossible alternative up-titration of brolucizumab.

Aflibercept in the maintenance phase until Week 32

As already described in dossier assessment A23-101 [1], based on the information in the clinical study report, 17.9% of patients had not been treated according to the current SPC for aflibercept [8] at Week 32. 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]. The company did not address the control arm in its dossier. In its comments [2], the company argues that, following the amendment of the study protocol of the TALON study, not all SPC-compliant dosing regimens during the maintenance phase for treatment with aflibercept were reflected in the study. This means that all patients who were still being treated with aflibercept in the TALON study after the change to the study protocol were potentially affected. According to the company, patients who were treated with aflibercept at an 8-week interval after the study protocol amendment might have needed a 4-week interval. This reasoning of the company is not appropriate. According to the study protocol (after the study protocol amendment), all patients who would have required a 4-week dosing interval in the maintenance phase had to discontinue the study treatment. After discontinuation of the study medication, these patients could then have received aflibercept as follow-up therapy every 4 weeks. As described above, only 17.9% of patients in the aflibercept arm had to discontinue study treatment by Week 32 due to a required 4-week dosing interval in the maintenance phase. For the remaining patients in the aflibercept arm, it can be assumed that they were adequately treated with their respective dosing interval. The data on Week 32 are therefore suitable for the present benefit assessment.

Conclusion

In summary, by Week 32, more than 80% of all patients included in both treatment arms were treated in sufficient accordance with the SPC. The data of the TALON study at Week 32 are therefore used for the benefit assessment. The remaining uncertainty regarding the non SPC-compliant use of brolucizumab is taken into account in the assessment of the certainty of conclusions (see also Section 2.2.2).

Patient characteristics

Table 2 shows the patient characteristics of the included study.

Table 2: Characteristics of the study populations as well as discontinuation of the study/therapy – RCT, direct comparison: brolucizumab vs. aflibercept

Study characteristic category	Brolucizumab N[a] = 366	Aflibercept N[a] = 368
TALON		
Age [years], mean (SD)	76 (8)	76 (8)
Sex [F/M], %	59/41	55/45
Family origin, n (%)		
White	310 (85)	312 (85)
Black or African American	1 (< 1)	1 (< 1)
Asian	55 (15)	55 (15)
Others[b]	43 (12)	39 (11)
Disease duration: time since nAMD diagnosis, n (%)		
< 1 month	290 (79)	283 (77)
1–3 months	44 (12)	44 (12)
≥ 3 months	32 (9)	41 (11)
Best-corrected visual acuity, mean (SD)	63.9 (12.1)	63.6 (12.0)
Best-corrected visual acuity category, n (%)		
≤ 54 letters	75 (21)	94 (26)
55 to ≤ 73 letters	200 (55)	188 (51)
≥ 74 letters	88 (24)	85 (23)
Central Subfield Foveal Thickness (CSFT) [µm], mean (SD)	443.8 (164.5)	467.0 (163.3)
CNV lesion category, n (%)	N = 324	N = 329
Type 1	158 (49)	166 (51)
Type 2	125 (39)	116 (35)
Type 3	40 (12)	46 (14)
Not determinable or missing	1 (< 1)	1 (< 1)
Treatment discontinuation by Week 32 n (%)[c]	67 (18)	91 (25)
Study discontinuation by Week 32, n (%)[d]	29 (8)	34 (9)

a. Full analysis set population of the company, defined as all randomized patients who received at least one dose of the study medication. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation, summarized from the categories of Chinese, Indian and Korean.
c. Common reasons for treatment discontinuation in the intervention versus the control arm were: Sponsor Request (9% vs. 18%), adverse event (4% vs. 1%), discontinuation at the patient's request (4% vs. 5%).
d. Common reasons for study discontinuation in the intervention versus the control arm were: discontinuation at the patient's request (5% versus 7%), decision by the investigator (1% versus 2%).

CNV: choroidal neovascularization; CSFT: Central Subfield Foveal Thickness; f: female; m: male; n: number of patients in the category; N: number of randomized patients who had received at least one dose of the study medication; nAMD: neovascular age-related macular degeneration; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics were balanced between the study arms. The majority of patients were of White ancestry, and their average age was 76 years. Slightly less than half were women. Almost a quarter of the patients had a best-corrected visual acuity of at least 74 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. For the majority (approx. 78%) of patients, the time between diagnosis of nAMD and inclusion in the study was less than 1 month.

Treatment discontinuations occurred more frequently in the control arm (25%) than in the intervention arm (18%). The number of study discontinuations is comparable between the arms (8% vs. 9%).

Risk of bias across outcomes (study level)

Table 3 shows the risk of bias across outcomes (risk of bias at study level).

Table 3: 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			
TALON	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the TALON study.

Transferability of the study results to the German health care context

Since the company did not use the TALON study for the benefit assessment, it also presented no information on the transferability of the study results to the German health care context.

2.2 Results on added benefit

2.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity

- Best corrected visual acuity (BCVA) (measured using ETDRS vision charts)
- health status (recorded with the National Eye Institute Visual Functioning Questionnaire-25 [NEI VFQ-25], general health subscale)

- Health-related quality of life
  - Health-related quality of life (recorded using NEI VFQ-25)
- Side effects
  - Serious adverse events (SAEs)
  - Discontinuation due to adverse events (AEs)
  - intra-ocular inflammation (including endophthalmitis and retinal vascular occlusion; operationalized as ocular AEs of special interest [AESI])
  - serious intra-ocular inflammation (including endophthalmitis and retinal vascular occlusion) operationalized as ocular SAEs)
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which did not present any data for the benefit assessment. However, in the subsequently submitted documents, the company presents analyses on further outcomes.

Table 4 shows the outcomes for which data are available in the included study.

Table 4: Matrix of outcomes – RCT, direct comparison: brolucizumab vs. aflibercept

Study	Outcomes								
	All-cause mortality	Best corrected visual acuity[a]	Health status (NEI VFQ-25, general health subscale)	Health-related quality of life (NEI VFQ-25)	SAEs	Discontinuation due to AEs	intra-ocular inflammation[b]	Serious intra-ocular inflammation[c]	Other specific AEs
TALON	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]

a. Result refers to the study eye.
b. Including endophthalmitis and retinal vascular occlusion; operationalized as ocular AESI.
c. Including endophthalmitis and retinal vascular occlusion; operationalized as ocular SAEs.
d. Suitable (incomplete) analyses on AEs are not available, a choice of further specific AEs was therefore impossible. On the basis of the available, incomplete analyses, no further specific AEs would be identified from the AEs that occurred, see also the following text.

AE: adverse event; AESI: adverse event of special interest; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event

Notes on the included outcomes and analyses

Best corrected visual acuity

In the TALON study, BCVA was measured using ETDRS vision charts at an initial distance of 4 meters. A 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 letter size decreases with each row.

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 equals the number of correctly read letters. The BCVA values can range from 0 to 100. Higher values mean better visual acuity.

The company presented analyses on both the improvement and the deterioration of the BCVA. In the present therapeutic indication, a (partially irreversible) deterioration in visual acuity up to blindness can occur due to the progression of the disease [9]. Among other things, an improvement of visual acuity might be due to a reduction of fluid in the eye and hence an improved physiological function of the eye [10,11]. In the present therapeutic indication, analyses of both improvement and deterioration of best corrected visual acuity are therefore taken into account.

In line with the reasons described in the benefit assessments of ocriplasmin [12,13], the responder analysis on the improvement or deterioration by ≥ 10 ETDRS letters (corresponds to 2 lines) was used for the present benefit assessment. The responder analysis of improvement or deterioration by ≥ 15 ETDRS letters (corresponds to 3 rows) is presented as supplementary information. According to the study protocol, patients who had a BCVA of ≥ 84 ETDRS letters at Week 32 were also considered responders in addition to patients with an increase in BCVA of ≥ 10 or ≥ 15 ETDRS letters. This means that patients with a baseline value of > 74 ETDRS letters had to achieve an improvement of less than 10 ETDRS letters to be counted as responders. 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. Based on the baseline values of the patients included, however, it cannot be assumed in the present data situation that this proportion of patients has a relevant effect on the result.

NEI VFQ-25

The NEI VFQ-25 is a questionnaire for surveying vision-related quality of life; it consists of a total of 26 items and 12 subscales [14]. Among these, 25 items (11 subscales) concern vision, and 1 item (1 subscale) surveys general health.

The scores for all items are transformed to arrive at a score of 0 to 100, and for each subscale, an average score is calculated based on all the items of the subscale. Ultimately, the sum score is calculated from the mean of the averaged subscale scores. The subscale on general health is disregarded in this process. The NEI VFQ-25 sum score can range from 0 to 100, with higher scores indicating better vision-related quality of life.

For the outcome of health-related quality of life, the company presents post hoc responder analyses on the change in the sum score of the NEI VFQ-25 and the 12 subscales by 15 points each (corresponds to 15 % of the scale range). The data do not reveal whether only the improvement or the deterioration or a combined analysis is meant. However, in Appendix III [15] attached to the subsequently submitted data, the company speaks of an improvement. It is therefore assumed that the analyses presented for the NEI VFQ-25 each represent an improvement by ≥ 15 points. The company did not present responder analyses on the deterioration of the NEI VFQ-25 by ≥ 15 points. However, both improvement and deterioration are relevant in the present indication. Therefore, the present assessment relies on the continuous analyses where available. Where no continuous analyses are available, the improvement by ≥ 15 points is used.

The subscale on general health (1 item) is assigned to the category of morbidity.

(Serious) intra-ocular inflammation (including endophthalmitis and retinal vascular occlusion)

In the clinical study report, the company defines ocular AESI as events from the categories of endophthalmitis, intra-ocular inflammation and retinal vascular occlusion. A complete list of the events included in the ocular AESIs is not available. Moreover, it is unclear whether these were predefined. However, based on the events that actually occurred, it is assumed that this summary adequately reflects the specific side effects of brolucizumab that also led to the safety measure and study protocol amendment in the TALON study (intra-ocular inflammation including retinal vasculitis and retinal vascular occlusion). For the present benefit assessment, the ocular AESI are therefore used as a suitable operationalization for the outcome of intra-ocular inflammation. Consequently, the operationalization of serious ocular AESI would also have been preferred for the outcome of severe intra-ocular inflammation, for which, however, no data are available. Since the overall rate of ocular SAEs largely includes events that also correspond to an ocular AESI, the ocular SAEs are used as a suitable operationalization for serious intra-ocular inflammation for the present benefit assessments.

Last interval without disease activity

In its subsequently submitted data, the company presents analyses on the primary outcome "last interval without disease activity" (these analyses correspond to those from the clinical study report). The company describes that in the brolucizumab arm, more patients could be treated with a dosing interval of 12 weeks without disease activity occurring compared to the aflibercept arm. However, a longer dosing interval is not per se patient-relevant. The primary treatment goal is to achieve a condition without disease activity. Possible advantages of a longer dosing interval, such as fewer side effects or better treatment adherence, are depicted by recording the AEs or other patient-relevant outcomes in the categories of morbidity and/or health-related quality of life. The outcome of last interval without disease activity was therefore disregarded in the present benefit assessment.

Irrespective of the suitability of the operationalization of disease activity presented, the submitted data do not provide any information on how many of the patients had no disease activity at Week 32.

Choice of further specific AEs

Analyses of all occurred AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT) are not available for Week 32. In the data subsequently submitted, the company subdivided the presentation of AEs and SAEs that occurred (categorized by SOC and PT) into ocular and non-ocular AEs. The company divides the ocular AEs by study eye or the other eye, so that no aggregated analysis of all ocular AEs is available. Only events that occurred in at least 10 patients were included in this subdivided presentation. As a result, it is not possible to add up the events that occurred in the study eye or the other eye. However, individual PTs or SOCs

that occurred in less than 10 patients in the subdivided analysis and were therefore not presented could exceed this threshold value in total (study eye + other eye) and would therefore be relevant for the selection of specific AEs (e.g. the ocular AE "conjunctival haemorrhage" [PT] in the study eye occurred in of 17 (4.6%) patients in the brolucizumab arm; in the aflibercept arm, in contrast, this AE occurred in 8 (2.2%) of patients in (p = 0.065). In the other eye, this PT apparently occurred in less than 10 patients and was therefore not shown. However, even a relatively low number of events (< 10) in the other eye could lead to a significant difference between the treatment arms in this PT when the study eye and the other eye are considered together). Complete analyses on the ocular AEs and SAEs are not provided in the clinical study report either. Therefore, no suitable data are available for the selection of specific AEs based on the events that occurred in the study. Irrespective of this, the (separate and incomplete) presentation provided by the company shows no statistically significant differences between the treatment arms for either ocular or non-ocular AEs and SAEs.

2.2.2 Risk of bias

Table 5 describes the risk of bias for the results of the relevant outcomes.

Table 5: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: brolucizumab versus aflibercept

Study		Outcomes								
	Study level	All-cause mortality	Best corrected visual acuity[a]	Health status (NEI VFQ-25, general health subscale)	Health-related quality of life (NEI VFQ-25)	SAEs	Discontinuation due to AEs	intra-ocular inflammation[b]	Serious intra-ocular inflammation[c]	Other specific AEs
TALON	L	L	H[d]	H[e]	H[e]	L	L	L	L	–

a. Result refers to the study eye.
b. Including endophthalmitis and retinal vascular occlusion; operationalized as ocular AESI.
c. Including endophthalmitis and retinal vascular occlusion; operationalized as ocular SAEs.
d. Unclear proportion of LOCF-imputed values.
e. High proportion of patients not considered in the analysis (> 10%).

AE: adverse event; AESI: adverse event of special interest; H: high; L: low; LOCF: last observation carried forward; NEI VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event

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

The risk of bias of the results on the outcome of BCVA was rated as high because the proportion of values imputed using last observation carried forward (LOCF) for these outcomes was unclear. By week 32, 8% of patients in the intervention arm and 9% in the comparator arm had discontinued the study prematurely. Whether or how many values were missing or imputed for the outcome of BCVA at Week 32, at what time point the last observed value was available for the patients with imputed values and whether this unknown proportion of missing values is balanced between the treatment arms cannot be inferred from the company's documents.

For the outcomes of health status (NEI VFQ-25 general health subscale) and health-related quality of life (NEI VFQ-25), there is a high proportion of missing values (for the responder analyses just under 30% without relevant differences between the treatment groups), which leads to a high risk of bias in the results for these outcomes. In addition, there are discrepancies between the clinical study report and the data subsequently submitted by the company regarding the number of patients included in the analyses. According to the study report, a score for the NEI VFQ-25 (sum score) at baseline and at Week 32 was available for 278 patients in the intervention arm. In the control arm, this applied to 261 patients. In contrast, only 266 and 250 patients respectively were included in the subsequently submitted responder analyses on the improvement in the NEI VFQ-25 (sum score) at Week 32. This discrepancy is particularly problematic for the outcome of health status (NEI VFQ-25, general health subscale), which narrowly missed the statistical significance (see Section 2.2.3).

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under the risk of bias, the certainty of conclusions of study results is in principle initially limited due to the uncertainties described in Section 2.1 regarding the administration of brolucizumab in compliance with the SPC. However, for the outcomes of all-cause mortality, discontinuation due to AEs, intra-ocular inflammation and serious intra-ocular inflammation, the study report shows that only a few patients with event in the respective outcome received a significantly shorter dosing interval than 8 weeks in the maintenance phase (> 4 days deviation from 56 days). It can also be seen that in most cases important deviations only occurred once during the course of the study (see also Appendix C). The results or observed effects are therefore not relevantly influenced by patients who had important deviations from the SPC for brolucizumab in the brolucizumab arm during the maintenance phase. On the basis of the available information, at most indications, e.g. of an added benefit, can therefore be determined for the outcomes of discontinuation due to AEs, ocular AESI and ocular SAEs. Since 1 out of a total of 4 events for the outcome "all-cause mortality" occurred in a patient with a clearly undercut dosing interval, at most a hint, e.g. of

an added benefit, can be determined for this outcome (see also Appendix C). Based on the available information, at most hints, e.g. of an added benefit, can be determined for the outcomes of BCVA, health status (NEI VFQ-25 general health subscale) and health-related quality of life (NEI VFQ-25) due to high risk of bias and the described uncertainties.

2.2.3 Results

Table 6 and Table 7 summarize the results on the comparison of brolucizumab with aflibercept in adult patients with nAMD. Where necessary, IQWiG calculations are provided to supplement the data.

Tables on common AEs, common SAEs and discontinuations due to AEs are presented in Appendix A. Results of the responder analyses for the outcome of health-related quality of life are presented in Appendix B.

Table 6: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brolucizumab vs. aflibercept (multipage table)

Study outcome category outcome	Brolucizumab		Aflibercept		Brolucizumab vs. aflibercept
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
TALON (Week 32)					
Mortality					
All-cause mortality	366	4[b] (1.1)	368	0	9.05 [0.49; 167.47]; 0.045[c]
Morbidity					
Best corrected visual acuity					
Improvement by ≥ 10 ETDRS letters[d]	366	144 (39.3)	368	131 (35.6)	1.11 [0.92; 1.33]; 0.295
Deterioration by ≥ 10 ETDRS letters[d]	366	22 (6.0)	368	26 (7.1)	0.85 [0.49; 1.47]; 0.564
Improvement by ≥ 15 ETDRS letters[d] (*presented as supplementary information*)	366	88 (24.0)	368	92 (25.0)	0.96 [0.75; 1.24]; 0.763
Deterioration by ≥ 15 ETDRS letters[d] (*presented as supplementary information*)	366	16 (4.4)	368	18 (4.9)	0.89 [0.46; 1.73]; 0.738
NEI VFQ-25[e]					
General health subscale; improvement by ≥ 15 points	266	47 (17.7)	250	61 (24.4)	0.72 [0.52; 1.02]; 0.062
General health subscale; deterioration by ≥ 15 points	No data available				

Table 6: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brolucizumab vs. aflibercept (multipage table)

Study outcome category outcome	Brolucizumab N	Brolucizumab patients with event n (%)	Aflibercept N	Aflibercept patients with event n (%)	Brolucizumab vs. aflibercept RR [95% CI]; p-value[a]
Side effects					
AEs[e] (supplementary information)	366	200 (54.6)	368	200 (54.3)	–
SAEs	366	39 (10.7)	368	31 (8.4)	1.26 [0.81; 1.98]; 0.305
Discontinuation due to AEs	366	18 (4.9)	368	3 (0.8)	6.03 [1.79; 20.31]; 0.004
Intra-ocular inflammation[f, g]	366	20 (5.5)	368	4 (1.1)	5.03 [1.74; 14.56]; < 0.001[c]
Serious intra-ocular inflammation[g, h]	366	8 (2.2)	368	2 (0.5)	4.02 [0.86; 18.81]; 0.057[c]

a. Wald test.
b. 2 patients died from cardiac disorders (cardiac arrest and acute myocardial infarction) and 2 in connection with COVID-19.
c. Institute's calculation, unconditional exact test (CSZ method according to [16]).
d. Proportion of patients with an increase or decrease in BCVA by ≥ 10 ETDRS letters (or by ≥ 15 ETDRS letters, presented as supplementary information) from baseline at Week 32, at a scale range of 0 to 100. Higher (increasing) values indicate an improvement of symptoms.
e. Includes events due to the underlying illness. Given the available data, however, the analyses are usable because the disease-related events included in the respective analyses presumably do not impact study results in a relevant manner.
f. Including endophthalmitis and retinal vascular occlusion; operationalized as ocular AESI.
e. Refers to the study eye.
h. Including endophthalmitis and retinal vascular occlusion; operationalized as ocular SAEs.

AE: adverse event; AESI: adverse event of special interest; CI: confidence interval; COVID-19: coronavirus disease 2019; ETDRS: Early Treatment Diabetic Retinopathy Study; n: number of patients with (at least one) event; N: number of analysed patients; NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 7: Results (health-related quality of life, continuous) – RCT, direct comparison: brolucizumab versus aflibercept

Study outcome category outcome	Brolucizumab			Aflibercept			Brolucizumab vs. aflibercept
	N[a, b]	values at baseline mean (SD)	change at Week 32 mean[c] (SD)	N[a, b]	values at baseline mean (SD)	change at Week 32 mean[c] (SD)	MD [95% CI]; p-value[c]
TALON							
Morbidity							
NEI VFQ-25[d]							
General health status subscale					N D		
Health-related quality of life							
NEI VFQ-25[d]							
Sum score	278	N D	4.09	261	N D	3.72	0.37 [-0.2; 0.9]; 0.193
Problems with colour vision	278	N D	1.78	258	N D	0.02	1.76 [-0.0; 3.5]
Dependence on others	278	ND	2.71	261	ND	2.22	0.49 [-2.0; 3.0]
Distance vision	278	ND	3.06	261	ND	3.78	-0.71 [-3.4; 2.0]
Driving problems	167	ND	4.92	164	ND	4.19	0.73 [-3.6; 5.1]
General vision	278	ND	7.94	261	ND	5.79	2.16 [-0.3; 4.6]
Mental condition	278	ND	5.83	261	ND	6.79	-0.96 [-3.8; 1.8]
Near vision	278	ND	7.46	261	ND	5.86	1.60 [-1.4; 4.6]
Eye pain	278	ND	3.55	261	ND	2.78	0.77 [-1.8; 3.4]
Peripheral vision	277	ND	3.24	261	ND	2.00	1.24 [-1.6; 4.1]
Exercising social roles	278	ND	5.17	261	ND	4.30	0.88 [-2.8; 4.6]
Social functioning	278	ND	1.99	261	ND	0.43	1.55 [-0.7; 3.8]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Discrepancy between data in the subsequently submitted Appendix and Module 5. The data presented are from Module 5.
c. Pairwise ANCOVA model with treatment as a fixed effect factor and corresponding baseline value of the outcome as covariate.
d. Higher (increasing) values indicate better symptoms/health-related quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).

ANCOVA: analysis of covariance; CI: confidence interval; MD: mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

Based on the available information, at most indications, e.g. of an added benefit, can be determined for the outcomes of all-cause mortality discontinuation due to AEs and (serious)

intra-ocular inflammation including endophthalmitis and retinal vascular occlusion. At most hints, e.g. of an added benefit, can be determined for the outcomes of BCVA, health status (NEI VFQ-25 general health subscale) and health-related quality of life (NEI VFQ-25) due to the high risk of bias and the described uncertainties.

Mortality

All-cause mortality

A statistically significant difference to the disadvantage of brolucizumab was shown for the outcome "all-cause mortality". This result was based on few events overall observed in the study. For the outcome "all-cause mortality", this results in a hint of greater harm from brolucizumab compared to aflibercept.

Morbidity

BCVA

No statistically significant difference between the treatment groups was shown for the outcome of BCVA (responder analysis on improvement or deterioration by ≥ 10 ETDRS letters). There was no hint of an added benefit of brolucizumab in comparison with aflibercept; an added benefit is therefore not proven.

Health status (NEI VFQ-25, general health subscale)

There was no statistically significant difference between treatment groups regarding the outcome of health status (recorded with the VFQ-25 VAS, general health subscale). There was 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 (sum score)

No statistically significant difference between treatment groups was found for the outcome of health-related quality of life (recorded using the NEI VFQ-25 summary score). There was no hint of an added benefit of brolucizumab in comparison with aflibercept; an added benefit is therefore not proven.

Side effects

SAEs and serious intra-ocular inflammation (including endophthalmitis and retinal vascular occlusion)

No statistically significant difference between treatment groups was shown for the outcomes of SAEs or serious intra-ocular inflammation. Hence, there is no hint of greater or lesser harm from brolucizumab in comparison with aflibercept for any of them; greater or lesser harm is therefore not proven.

Discontinuation due to AEs and intraocular inflammation (including endophthalmitis and retinal vascular occlusion)

A statistically significant difference to the disadvantage of brolucizumab was shown for the outcomes "discontinuation due to AEs" and “intra-ocular inflammation”. For each of them, there is an indication of greater harm from brolucizumab in comparison with aflibercept.

2.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account in the present assessment:

- Age (< 75 years vs. ≥ 75 years)
- Sex (female versus male)
- BCVA (≤ 54 ETDRS letters vs. 55-73 ETDRS letters vs. ≥ 74 ETDRS letters)

The documents subsequently submitted by the company and Module 5 contain no interaction tests and no subgroup analyses for the outcome categories of mortality, morbidity, health-related quality of life and ocular AESI.

Interaction tests for the remaining outcomes are performed when 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 one subgroup.

Only the results with 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.

Using the methods described above, the available subgroup results did not show any relevant effect modifications.

2.3 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 [17].

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.

2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.2.3 (see Table 8).

Determination of the outcome category for the outcomes on side effects

Discontinuation due to AEs

The outcome of discontinuation due to AEs was assigned to the outcome category of non-serious/non-severe side effects. The information in the clinical study report shows that in the brolucizumab arm, 6 of the total of 18 AEs that led to discontinuation of treatment by Week 32 were SAEs. Based on the data in the study report, it can be assumed that 1 of the 3 AEs in the aflibercept arm that led to discontinuation of treatment was an SAE. Overall, therefore, less than half (33%) of all AEs that led to discontinuation of treatment were SAEs. The company presented no assessment regarding the severity grade of this outcome.

Intra-ocular inflammation (including endophthalmitis and retinal vascular occlusion)

The outcome of intra-ocular inflammation was therefore also assigned to the outcome category of non-serious/non-severe side effects. The information in the study report shows that 7 of the 20 ocular AESIs that occurred in the brolucizumab arm up to Week 32 were SAEs. For the aflibercept arm, 2 of the 4 ocular AESIs were an SAE. Overall, less than half (38%) of the ocular AESIs are therefore SAEs. The company presented no assessment regarding the severity grade of this outcome.

Table 8: Extent of added benefit at outcome level: brolucizumab versus aflibercept (multipage table)

Outcome category **outcome**	**Brolucizumab vs. aflibercept** **proportion of events (%) or MD** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality (Week 32)		
All-cause mortality	1.1 vs. 0 RR: 9.05 [0.49; 167.47]; RR: 0.11 [0.01; 2.04][c] p = 0.045 probability: "hint"	Outcome category: mortality greater harm, extent: minor[d]
Morbidity (Week 32)		
BCVA (improvement by ≥ 10 ETDRS letters)	39.3 vs. 35.6 RR: 1.11 [0.92; 1.33]; p = 0.295	Lesser/added benefit not proven
BCVA (deterioration by ≥ 10 ETDRS letters)	6.0 vs. 7.1 RR: 0.85 [0.49; 1.47]; p = 0.763	
Health status (NEI VFQ-25, general health subscale; improvement by ≥ 15 points)	17.7 vs. 24.4 RR: 0.72 [0.52; 1.02]; p = 0.062	Lesser/added benefit not proven
Health status (NEI VFQ-25, general health subscale; deterioration by ≥ 15 points)	N D	
Health status (NEI VFQ-25, general health subscale, continuous analysis)	N D	
Health-related quality of life (Week 32)		
NEI VFQ-25 (sum score, continuous analysis)	4.09 vs. 3.72 MD: 0.37 [-0.2; 0.9]; p = 0.193	Lesser/added benefit not proven
Side effects (Week 32)		
SAEs	10.7 vs. 8.4 RR: 1.26 [0.81; 1.98]; p = 0.305	Greater/lesser harm not proven
Discontinuation due to AEs	4.9 vs. 0.8 RR: 6.03 [1.79; 20.31]; RR: 0.17 [0.05; 0.56][c]; p = 0.004 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: "considerable"

Table 8: Extent of added benefit at outcome level: brolucizumab versus aflibercept (multipage table)

Outcome category **outcome**	**Brolucizumab vs. aflibercept** **proportion of events (%) or MD** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Intra-ocular inflammation	5.5 vs. 1.1 RR: 5.03 [1.74; 14.56]; RR: 0.20 [0.07; 0.57][c]; p < 0.001 probability: “indication”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm; extent: “considerable”
Serious intra-ocular inflammation	2.2 vs. 0.5 RR: 4.02 [0.86; 18.81]; p = 0.057	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The result of the statistical test is determinative for the derivation of added benefit. Its extent is rated as “minor”.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; MD: mean difference; ND: no data; NEI VFQ-25: National Eye Institute Function Questionnaire-25; RR: relative risk; SAE: serious adverse event

2.3.2 Overall conclusion on added benefit

Table 9 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 9: Positive and negative effects from the assessment of brolucizumab compared to aflibercept

Positive effects	**Negative effects**
–	Mortality ▪ all-cause mortality: hint of greater harm – extent: "minor"
–	Non-serious/non-severe side effects ▪ discontinuation due to AEs: indication of greater harm – extent: “considerable” ▪ intra-ocular inflammation (including endophthalmitis and retinal vascular occlusion): indication of greater harm - extent: “considerable”
No data on deterioration are available for the outcome "health status". No suitable data are available for the choice of further specific AEs.	
AE: adverse event	

Overall, there are only negative effects of different severities. For all-cause mortality, there was a statistically significant effect to the disadvantage of brolucizumab compared to aflibercept with the extent “minor”. However, only a few events occurred: 4 deaths in the intervention arm (2 patients died of cardiac disorders and 2 in connection with COVID-19). For the outcomes of discontinuation due to AEs and intra-ocular inflammation (including endophthalmitis and retinal vascular occlusion), there is an indication of greater harm with considerable extent in each case.

In the overall consideration of the available results, the negative effects lead to the derivation of lesser benefit.

In summary, there is an indication of lesser benefit from brolucizumab versus aflibercept for adult patients with nAMD.

2.4 Summary

The information and data subsequently submitted by the company in the commenting procedure cause the TALON study to be used for the benefit assessment and change the conclusion on the added benefit of brolucizumab from dossier assessment A23-101:

Table 10 below shows the result of the benefit assessment of brolucizumab, taking into account dossier assessment A23-101 and the present addendum.

Table 10: 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	Indication of lesser benefit
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.

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Appendix A Results on side effects

The tables below present events for Medical Dictionary for Regulatory Activities (MedDRA) SOCs and PTs for the overall rates of AEs and SAEs, each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in one study arm
- Overall rate of SAEs: events that occurred in at least 5% of patients in one study arm
- Additionally, for all events irrespective of severity: events which occurred in at least 10 patients and at least 1% of patients in 1 study arm

For the outcome of discontinuation due to AEs, all events (SOC/PT) that resulted in discontinuation are completely presented.

Table 11: Common AEsa – RCT, direct comparison: brolucizumab versus aflibercept

Study	Patients with event n (%)	
SOC[b] PT[b]	Brolucizumab N = 366	Aflibercept N = 368
TALON		
Overall rate of ocular AEs Study eye	107 (29)	96 (26)
Eye disorders	100 (27)	87 (24)
Conjunctival haemorrhage	17 (5)	8 (2)
Dry eye	6 (2)	14 (4)
Eye pain	12 (3)	10 (3)
Visual acuity reduced	13 (4)	13 (4)
Vitreous floaters	10 (3)	4 (1)
Overall rate of ocular AEs other eye	46 (13)	65 (18)
Eye disorders	42 (12)	59 (16)
Dry eye	4 (1)	11 (3)
Neovascular age-related macular degeneration	12 (3)	12 (3)
Overall rate of non-ocular AEs	149 (41)	142 (39)
Cardiac disorders	14 (4)	6 (2)
Gastrointestinal disorders	20 (6)	12 (3)
General disorders and administration site conditions	7 (2)	10 (3)
Infections and infestations	45 (12)	48 (13)
Injury, poisoning and procedural complications	21 (6)	23 (6)
Investigations	12 (3)	10 (3)
Metabolism and nutrition disorders	16 (4)	21 (6)
Musculoskeletal and connective tissue disorders	25 (7)	24 (7)
Nervous system disorders	23 (6)	27 (7)
Skin and subcutaneous tissue disorders	11 (3)	6 (2)
Vascular disorders	20 (6)	19 (5)
Hypertension	13 (4)	14 (4)

a. Events that occurred in ≥ 10 patients in at least one study arm. However, the company presents the events that occurred separately by study eye and other eye (see Section 2.2.1).
b. MedDRA version 24.0; PT notation taken without adaptation from the data subsequently submitted by the company.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial

Table 12: Common SAEsa – RCT, direct comparison: brolucizumab versus aflibercept

Study	**Patients with event n (%)**	
SOC PT	**Brolucizumab N = 366**	**Aflibercept N = 368**
TALON		
Total rate of non-ocular SAEs[b]	31 (9)	29 (8)

a. Events that occurred in ≥ 10 patients in at least one study arm. However, the company presents the events that occurred separately by study eye and other eye (see Section 2.2.1).
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse events; SOC: System Organ Class

Table 13: Discontinuation due to AEs – RCT, direct comparison: brolucizumab versus aflibercept

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Brolucizumab** **N = 366**	**Aflibercept** **N = 368**
TALON		
Overall rate of discontinuations due to AEs	18 (4.9)	3 (0.8)
Cardiac disorders	1 (0.3)	0 (0)
Cardiac arrest	1 (0.3)	0 (0)
Eye disorders	15 (4.1)	1 (0.3)
Eye inflammation	1 (0.3)	0 (0)
Iridocyclitis	1 (0.3)	0 (0)
Ocular myasthenia	1 (0.3)	0 (0)
Retinal artery occlusion	3 (0.8)	0 (0)
Retinal occlusive vasculitis	2 (0.5)	0 (0)
Retinal vascular occlusion	1 (0.3)	0 (0)
Retinal vasculitis	1 (0.3)	0 (0)
Retinal vein occlusion	0 (0)	1 (0.3)
Uveitis	3 (0.8)	0 (0)
Vitritis	2 (0.5)	0 (0)
Infections and infestations	2 (0.5)	1 (0.3)
COVID-19	1 (0.3)	0 (0)
Endophthalmitis	1 (0.3)	0 (0)
Infective exacerbation of chronic obstructive airways disease	0 (0)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0 (0)	1 (0.3)
Pancreatic carcinoma	0 (0)	1 (0.3)

a. MedDRA version 24.0; SOC and PT notation taken without adaptation from the documents provided by the company.

AE: adverse event; COVID-19: Coronavirus Disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; ND: no data; OCS: oral corticosteroids; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix B Supplementary presentation of results on health-related quality of life

Table 14: Results (health-related quality of life) – RCT, direct comparison: brolucizumab versus aflibercept

Study outcome category outcome	Brolucizumab		Aflibercept		Brolucizumab vs. aflibercept
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
TALON (Week 32)					
Health-related quality of life					
NEI VFQ-25[b] (improvement by ≥ 15 points)					
Sum score	266	31 (11.7)	250	35 (14.0)	0.83 [0.53; 1.31]; 0.426
Problems with colour vision	263	26 (9.9)	245	19 (7.8)	1.27 [0.72; 2.24]
Dependence on others	266	35 (13.2)	250	41 (16.4)	0.80 [0.53; 1.22]
Distance vision	266	62 (23.3)	250	62 (24.8)	0.94 [0.69; 1.28]
Driving problems	151	44 (29.1)	149	38 (25.5)	1.14 [0.79; 1.65]
General vision	266	116 (43.6)	250	96 (38.4)	1.14 [0.92; 1.40]
Mental condition	266	64 (24.1)	250	62 (24.8)	0.97 [0.72; 1.31]
Near vision	266	89 (33.5)	250	95 (38.0)	0.88 [0.70; 1.11]
Eye pain	266	44 (16.5)	250	38 (15.2)	1.09 [0.73; 1.62]
Peripheral vision	262	54 (20.6)	250	50 (20.0)	1.03 [0.73; 1.45]
Exercising social roles	266	64 (24.1)	250	54 (21.6)	1.11 [0.81; 1.53]
Social functioning	266	30 (11.3)	250	22 (8.8)	1.28 [0.76; 2.16]

a. Wald test.
b. Proportion of patients with an increase in the NEI VFQ-25 general health subscale or the sum score by ≥ 15 points (≥ 15% of the scale range) from baseline at Week 32, at a scale range of 0 to 100. Higher (increasing) values indicate an improvement in symptoms or health-related quality of life.

CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; NEI VFQ-25: National Eye Institute Visual Function Questionnaire-25; RCT: randomized controlled trial; RR: relative risk

Appendix C Number of patients with dosing intervals significantly shorter than 8 weeks and events in the outcomes of all-cause mortality, discontinuation due to AEs and (serious) intra-ocular inflammation

Table 15: Number of patients with significantly shorter dosing intervals in the brolucizumab arm

Study outcome category	**Brolucizumab**		
	Patients with event n (%) total population N = 366	**Patients with dosing intervals significantly shorter than 8 weeks in the maintenance phase and event in the respective outcome[a]**	
TALON (Week 32)		n	Number of days of the significantly shorter dosing interval(s)
All-cause mortality	4 (1.1)	1	42 days
Discontinuation due to AEs	18 (4.9)	1	28, 25, 35 days
Intra-ocular inflammation[b, c]	20 (5.5)	3	46 days
			31 days
			28, 25, 35 days
Serious intra-ocular inflammation[c, d]	8 (2.2)	1	28, 28 days

a. In the remaining patients with an event, the dosing interval in the maintenance phase was undercut by at most 4 days (52 days instead of 56).
b. Including endophthalmitis and retinal vascular occlusion; operationalized as ocular AESI.
c. Refers to the study eye.
d. Including endophthalmitis and retinal vascular occlusion; operationalised as ocular SUEs

AESI: adverse event of special interest; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SAE: serious adverse event