Medicinrådet

Bilag til direkte indplacering af aflibercept (8 mg) i Medicinrådets evidensgennemgang vedr. lægemidler til retinal veneokklusion

Vers. 1.0

Bilagsoversigt

1. Amgros' forhandlingsnotat vedr. aflibercept til retinal veneokklusion
2. Ansøgning vedr. aflibercept til retinal veneokklusion

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24.04.2026

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	27.05.2026
Leverandør	Bayer
Lægemiddel	Eylea (aflibercept)
Ansøgt indikation	Aflibercept 8 mg er indiceret til behandling af makulaødem sekundært til retinal veneokklusion (RVO) (grenveneokklusion eller centralveneokklusion)
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Eylea (aflibercept):

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Eylea	114,3 mg/ml (1 stk., hætteglas), svarer til 8 mg	5.132,01	[redacted]	[redacted]
Eylea	114,3 mg/ml (1 stk., sprøjte), svarer til 8 mg	5.132,01	[redacted]	[redacted]
Eylea	40 mg/ml (1 stk. sprøjte), svarer til 2 mg	4.918,73	[redacted]	[redacted]

Aftaleforhold

Amgros har en eksisterende aftale på Eylea. Aftalen løber indtil den 30.04.2027 med mulighed for 2x 6 måneders forlængelse. Eylea er en del af udbuddet af lægemidler til behandling af våd aldersrelateret maculadegeneration (Våd AMD), diabetisk maculaødem (DME) og retinal veneokkusion (RVO). Patentet på Eylea (aflibercept) er udløbet, og der indgår biosimilære lægemidler i udbuddet [redacted].

Konkurrencesituationen

Medicinrådet har en behandlingsvejledning og lægemiddelrekommandation for behandling af RVO, hvor Lucentis (ranibizumab), Eylea (aflibercept) og Vabysmo (faricimab) er ligestillet til patientpopulationen.

Medicinrådet anbefaler på nuværende tidspunkt Eylea med et behandlingsregime på 2 mg, til RVO. Denne vurdering vedrører et behandlingsregime med 8 mg. Medicinrådet vurderer, at Eylea 8 mg kan ligestilles ift. effekt og bivirkninger med de øvrige lægemidler, som indgår i Medicinrådets behandlingsvejledning.

Eylea 8 mg har også indikation til våd AMD og DME, og er anbefalet af Medicinrådet i denne styrke til begge indikationer.

I lægemiddelrekommandationen er der ikke angivet et førstevalg, og det er derfor op til den enkelte region at vurdere hvilken løsning, der er forbundet med de laveste omkostninger. Medicinrådet henviser i den sammenhæng til et støtteværktøj udarbejdet af Amgros. Af den årsag er der ikke lavet en sammenligning af lægemiddeludgifter mellem Lucentis, Eylea og Vabysmo.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
England	Anbefalet	Link til vurdering
Sverige	Ikke vurderet	

Opsummering

Eylea indgår i et udbud uden prisregulering på grund af biosimilær konkurrence, og leverandøren har derfor ikke mulighed for at tilbyde en lavere pris på nuværende tidspunkt.

Application for the assessment of aflibercept 8 mg by updating the “Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til retinal veneokklusion (RVO)”

Contact information

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Table of contents

Tables and Figures

Abbreviations

AAO	American Academy of Ophthalmology
AE(s)	Adverse event(s)
ANCOVA	Analysis of covariance
Ang-2	Angiopoietin-2
APTC	Anti-platelet trialists' collaboration
BCVA	Best corrected visual acuity
BL	Baseline
BMI	Body mass index
BRVO	Branch retinal vein occlusion
CFT	Central foveal thickness
CHO	Chinese hamster ovary
CI	Confidence interval
CKD	Chronic kidney disease
CMT	Central macular thickness
CRT	Central retinal thickness
CRV	Central retinal vein
CRVO	Central retinal vein occlusion
CST	Central subfield thickness
CVD	Cardiovascular disease
DEX implant	Dexamethasone implant
DF	Degrees of Freedom
DLip	Dyslipidemia
DM	Diabetes mellitus
DME	Diabetic macular oedema
DR	Diabetic retinopathy
EMA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein angiography
FAS	Full analysis set
FAZ	Foveal avascular zone
FP	Fundus photography

HR	Hazard ratio
HRVO	Hemi-retinal vein occlusion
ICE	Intercurrent Event
IOP	Intraocular pressure
IRF	Intraretinal fluid
IVFA	Intravenous fluorescein angiography
IVI(s)	Intravitreal injection(s)
LP	Laser photocoagulation
LS	Least Squares
MD	Mean difference
MMRM	Mixed model for repeated measurements
MO	Macular oedema
MoA	Mechanism of action
N/A	Not applicable
nAMD	Neovascular (wet) age-related macular degeneration
NEI	National Eye Institute
NEI VFQ-25	25-item National Eye Institute Visual Function Questionnaire
NMA	Network meta-analysis
NV	Neovascularization
NVG	Neovascular glaucoma
OC	Observed cases
OCT	Optical coherence tomography
OCTA	Optical coherence tomography-angiography
OR	Odds ratio
PACG	Primary angle closure glaucoma
PIGF	Placental growth factor
PRN	Pro re nata (as needed)
PRP	Prophylactic panretinal photocoagulation
PS	Protein S
Q4W (2q4)	Every 4 weeks
Q6W	Every 6 weeks
Q8W/3 (8q8/3)	Every 8 weeks; after 3 initial injections at 4-week intervals
Q8W/5 (8q8/5)	Every 8 weeks, after 5 initial injections at 4-week intervals
QoL	Quality of life
RCT(s)	Randomized clinical trial(s)
RVO	Retinal vein occlusion
SAEs	Serious adverse event(s)
SAF	Safety analysis set

SD	Standard Deviation
SE	Standard Error
SLR	Systematic literature review
SMPC	Summary of product characteristics
SoC	Standard of Care
SRF	Subretinal fluid
TE	Treat-and-extend
TEAE	Treatment emergent adverse events
TESAE	Treatment-emergent serious adverse event
UWFA	Ultra-widefield fluorescein angiography
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptors
VF	Visual function

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Eylea 8 mg
Generic name	Aflibercept 8 mg
Therapeutic indication as defined by EMA	Retinal vein occlusion
Marketing authorization holder in Denmark	Bayer A/S
ATC code	S01LA05
Combination therapy and/or co-medication	None
(Expected) Date of EC approval	16.1.2026
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Neovascular age related macular degeneration (nAMD) Diabetic macular edema
Other indications that have been evaluated by the DMC (yes/no)	Yes
Dispensing group	NA
Packaging – types, sizes/number of units and concentrations	Package with 1 vial containing aflibercept (114.3 mg/ml) (0.263 ml) Package with 1 pre-filled syringe containing aflibercept (114.3 mg/ml)

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Aflibercept 8 mg is indicated in adults for the treatment of retinal vein occlusion (branch retinal vein occlusion (BRVO) and central/hemi retinal vein occlusion (CRVO/HRVO))
Dosage regiment and administration:	Intravitreal injection of aflibercept 8 mg (0.07 ml) administered every 8 weeks after 3 initial injections at 4-week intervals (Q8W/3). Intravitreal injection of aflibercept 8 mg (0.07 ml) administered every 8 weeks after 5 initial injections at 4-week intervals (Q8W/5).
Choice of comparator [if any]	Intravitreal injection of aflibercept 2 mg (0.05 ml) administered every 4 weeks (Q4W).
Most important efficacy endpoints (Difference/gain compared to comparator)	At week 36, aflibercept 8 mg administered Q8W/3 or Q8W/5 demonstrated non-inferiority on the primary endpoint of change in best corrected visual acuity (BCVA) compared with aflibercept 2 mg Q4W; this non-inferiority was maintained at week 64 ○ The primary analysis endpoint was met: treatment with aflibercept 8 mg Q8W/3 or Q8W/5 demonstrated non-inferiority to aflibercept 2 mg Q4W, with mean changes in BCVA from baseline to week 36 of 17.4, 18.3 and 17.5 letters in the aflibercept 8 mg Q8W/3, aflibercept 8 mg Q8W/5 and aflibercept 2 mg Q4W groups, respectively At week 36 and 64, the proportion of patients losing ≥15 ETDRS letters were comparable between the dosing regimens with aflibercept 8 mg (Q8W/3 or Q8W/5) and aflibercept 2 mg Q4W. At week 36, aflibercept 8 mg administered Q8W/3 or Q8W/5 demonstrated comparable efficacy to aflibercept 2 mg Q4W in terms of improvement in vision-related quality of life, as measured by mean improvement in NEI VFQ-25 total score.
Most important serious adverse events for the intervention and comparator	The safety of aflibercept 8 mg administered Q8W/3 or Q8W/5 in the QUASAR trial was similar to the safety profile of aflibercept 2 mg and consistent with what was observed in previous clinical trials with aflibercept. No new safety signals were detected with aflibercept 8 mg formulation, and the incidence of serious events was very low: The proportion of patients with any ocular treatment-emergent adverse events through week 64 was similar across all 3 treatment groups (50.5% for aflibercept 8 mg Q8W/3, 44.3 %

Summary	
	for aflibercept 8 mg Q8W/5 and 47.2% for aflibercept 2 mg Q4W). The proportion of patients with an ocular treatment-emergent serious adverse event (SAE) in the study eye was low in all treatment groups (1.7% for aflibercept 8 mg Q8W/3, 1.7% for aflibercept 8 mg Q8W/5 and 2.7% for aflibercept 2 mg Q4W). . The rates of intraocular inflammation were 1.4% for aflibercept 8 mg Q8W/3 , 0.7% for aflibercept 8 mg Q8W/5 and 1.7% for aflibercept 2 mg Q4W through week 64.

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

Please, refer to the existing treatment guideline "Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til retinal veneokklusion (RVO)".

3.2 The intervention

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF. Because the binding affinity of aflibercept for VEGF-A isoforms and PlGF is higher than that of native receptors, VEGFR-1 and VEGFR-2, it effectively blocks VEGF binding and activation of native receptors [1]. This binding affinity is much higher than the native receptors, and the binding affinity of aflibercept to VEGF-A is shown to be stronger compared to other agents such as ranibizumab, bevacizumab, and brolucizumab [2,3].

VEGF-A and PlGF are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic and vascular permeability factors for endothelial cells [1]. VEGF-A is the major driver of abnormal angiogenesis, leading to ocular vascular diseases [3]. VEGF acts via 2 receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells [1]. PlGF binds only to VEGFR-1, which is also present on the surface of leukocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can act independently to activate the VEGFR-1 to promote an inflammatory response in the retina; it is also known to increase in pathological states such as nAMD, DR, DME and RVO [1].

The following substantial evidence supports the important role of VEGF in the pathogenesis of ocular neovascularisation:

- Injection of VEGF into the eye, or local overexpression of VEGF by transgenic methods, can induce vascular leaks and new blood vessel formation in the retina [4, 5]
- In animal models of CNV, blockade of VEGF signalling strongly suppresses the development of CNV, suggesting that VEGF is a necessary stimulus [6, 7]

- Likewise, VEGF blockade prevents or reverses neovascularisation in animal models of ischaemic retinopathy [8]
- In addition to VEGF itself, the related angiogenic protein, PlGF, has also been implicated in ocular neovascularisation [8]

CRVO has a higher VEGF load compared to other retinal diseases; therefore, ensuring the blocking of VEGF effects in CRVO is of significant importance [9].

Aflibercept 2 mg is a widely established effective first-line treatment option for RVO, broadly used in clinical practice and recommended in clinical guidelines [10-12]. Aflibercept 8 mg, which provides a 4-fold higher molar dose compared with aflibercept 2 mg, has been developed to increase VEGF suppression time and allow to extend treatment intervals without compromising treatment efficacy or patient safety while reducing treatment burden and the need for healthcare resources. Furthermore, improved treatment durability and reduced treatment burden are expected to improve patient adherence and, consequently short- and long-term visual outcomes in clinical practice.

Overview of intervention	
Therapeutic indication relevant for the assessment	Retinal vein occlusion – branch retinal vein occlusion (BRVO), hemiretinal vein occlusion (HRVO) and central retinal vein occlusion (CRVO)
Method of administration	Intravitreal injection
Dosing	Recommended dose is 8 mg of aflibercept, equivalent to 0.07 mL solution
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Treatment is initiated with 1 injection per month for 3 consecutive doses. Injection intervals may then be extended based on the physician's judgement of visual and/or anatomic outcomes.
Necessary monitoring, both during administration and during the treatment period	There is no requirement for monitoring between injections. Based on the physician's judgement, the schedule of monitoring visits may be more frequent than injection visits
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Not relevant

Overview of intervention	
Package size(s)	Package with 1 vial containing aflibercept (114.3 mg/ml) (0.263 ml) Package with 1 pre-filled syringe containing aflibercept (114.3 mg/ml)

3.2.1 The intervention in relation to Danish clinical practice

Treatment with aflibercept 8 mg is intended to be used in 1st line treatment of patients with retinal vein occlusion (RVO).

If the intervention is associated with diagnostic tests and methods used for patient selection that are not routinely applied in Danish clinical practice, please elaborate here.

Not applicable, as the intervention is already in use and is therefore not associated with any diagnostic tests and methods not already routinely applied in Danish clinical practice.

4. Overview of literature

Not relevant for the application, as the intervention is directly compared to the current standard of care in the provided study.

Table 1. Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
QUASAR study NCT05850520 Not published	QUASAR is a multicenter, randomized, double-masked, active-controlled, phase 3 study	The study consisted of a test (screening) phase, a treatment phase and an end-of-study phase. The pre-planned primary analysis was conducted at 36 weeks. Each participant was in the study for up to 64 weeks (up to 60 weeks in the treatment	Start: 15/5/2023 Primary completion: 7/11/2024 Study completion: 27/05/2025	Treatment of patients with retinal vein occlusion (BRVO, HRVO and CRVO).	Aflibercept 8 mg. Intravitreal administration. Dosing: Aflibercept 8 mg administered every 8 weeks (Q8W), after 3 initial injections at 4-week intervals Aflibercept 8 mg administered every 8 weeks (Q8W), after 5 initial injections at 4-week intervals	Aflibercept 2 mg. Intravitreal administration. Administered every 4 weeks (Q4W)	Not relevant	At week 36, aflibercept 8 mg administered Q8W/3 or Q8W/5 demonstrated non-inferiority on the primary endpoint of change in best corrected visual acuity (BCVA) compared with aflibercept 2 mg dosed Q4W; this non-inferiority was maintained at week 64 At week 36 and 64, the proportion of patient losing ≥15 ETDRS letters were comparable between the dosing regimens with aflibercept 8 mg Q8W/3 or Q8W/5 and aflibercept 2 mg Q4W. At week 36, aflibercept 8 mg administered Q8W/3 or Q8W/5 demonstrated comparable efficacy to aflibercept 2 mg Q4W in terms of improvement

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
		phase followed by a monitoring period until week 64).						in vision-related quality of life, as measured by mean improvement in NEI VFQ-25 total score. The safety of aflibercept 8 mg administered Q8W/3 or Q8W/5 in the QUASAR trial was similar to the safety profile of aflibercept 2 mg Q4W and consistent with what was observed in previous clinical trials with aflibercept. No new safety signals were detected with the aflibercept 8 mg formulation, and the incidence of serious events was very low.

* If there are several publications connected to a trial, include all publications used.

5. Clinical question(s) Is there any clinical significant difference between anti-VEGF agents for treatment of retinal vein occlusion (RVO)?

5.1 Efficacy of aflibercept 8 mg compared to aflibercept 2 mg in retinal vein occlusion.

5.1.1 Relevant studies

Overview of the phase 3 QUASAR study design

QUASAR is an ongoing multicenter, randomized, double-masked, active-controlled, phase 3 study of the efficacy and safety of aflibercept 8 mg compared with aflibercept 2 mg in participants with treatment-naïve MO secondary to RVO [13].

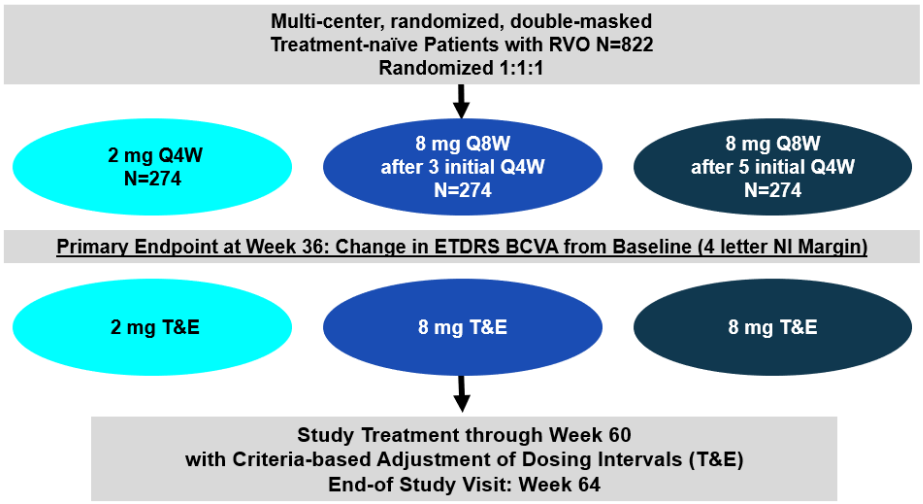
The primary objective of the study was to determine if treatment with aflibercept 8 mg at intervals of 8 weeks (after initial 3 or 5 monthly doses) provides non-inferior BCVA change compared with aflibercept 2 mg every 4 weeks, from the date of randomization through 36 weeks of treatment. The secondary objective was to determine if treatment with aflibercept 8 mg Q8W requires fewer injections compared to aflibercept 2 mg Q4W, potentially reducing the treatment burden for patients. The study also evaluates the safety and tolerability of aflibercept 8 mg.

The study consisted of a test (screening) phase, a treatment phase and an end-of-study phase. The pre-planned primary analysis was conducted at 36 weeks. Each participant was in the study for up to 64 weeks (up to 60 weeks in the treatment phase followed by a monitoring period until week 64).

In the trial, patients were randomized in a 1:1:1 ratio into three groups to receive either:

- aflibercept 8 mg administered with 3 initial monthly doses followed by an extension of treatment interval to 8 weeks (Q8W/3) and further adjustment of intervals according to treatment response;
- aflibercept 8 mg administered with 5 initial monthly doses followed by an extension of treatment interval to 8 weeks (Q8W/5) and further adjustment of intervals according to treatment response; or
- aflibercept 2 mg every 4 weeks (Q4W) until Week 32, followed by adjustment of intervals according to treatment response.

Figure 1. QUASAR study design



BCVA: Best-corrected Visual Acuity, ETDRS: Early Treatment of Diabetic Retinopathy Study, NI: non-inferiority, Q4W: every 4 weeks, Q8W: every 8 weeks, RVO: retinal vein occlusion, T&E: treat and extend

Patients in the aflibercept 8 mg groups can have their dosing intervals shortened to a minimum of every 4 weeks throughout the trial if protocol-defined criteria for disease progression are met. Dosing intervals may be extended based on protocol-defined criteria starting at week 32 for patients who receive aflibercept 2 mg or aflibercept 8 mg after 3 initial monthly doses or at week 40 for patients who receive aflibercept 8 mg after 5 initial monthly doses, with follow-up planned through week 64 (Figure 1).

5.1.2 Comparability of studies

Not relevant for the application, due to the study design comparing directly to an approved comparator.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Baseline demographics and disease characteristics of patients were balanced and comparable between study arms. The study arms were also well balanced with respect to the specific baseline disease characteristics of the study eye. The study population is considered to be comparable and eligible for Danish patients with nAMD.

Table 2 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	QUASAR Study				
	Aflibercept 2 mg Q4W n=301 (100%)	Aflibercept 8 mg			Total
		Q8W/3 n=293 (100%)	Q8W/5 n=298 (100%)	Pooled n=591 (100%)	n=892 (100%)
Sex, n (%)					
Female	144 (47.8%)	136 (46.4%)	146 (49.0%)	282 (47.7%)	426 (47.8%)
Male	157 (52.2%)	157 (53.6%)	152 (51.0%)	309 (52.3%)	466 (52.2%)
Race, n (%)					
American Indian or Alaska Native	0	0	2 (0.7%)	2 (0.3%)	2 (0.2%)
Asian	101 (33.6%)	91 (31.1%)	97 (32.6%)	188 (31.8%)	289 (32.4%)
Asian Indian	3 (1.0%)	2 (0.7%)	3 (1.0%)	5 (0.8%)	8 (0.9%)
Chinese	28 (9.3%)	31 (10.6%)	41 (13.8%)	72 (12.2%)	100 (11.2%)
Japanese	35 (11.6%)	32 (10.9%)	31 (10.4%)	63 (10.7%)	98 (11.0%)
Korean	25 (8.3%)	19 (6.5%)	15 (5.0%)	34 (5.8%)	59 (6.6%)
Thai	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)	5 (0.6%)
Other	8 (2.7%)	5 (1.7%)	6 (2.0%)	11 (1.9%)	19 (2.1%)
Black or African American	8 (2.7%)	7 (2.4%)	9 (3.0%)	16 (2.7%)	24 (2.7%)
White	178 (59.1%)	173 (59.0%)	177 (59.4%)	350 (59.2%)	528 (59.2%)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.3%)	1 (0.2%)	1 (0.1%)
Multiple*	1 (0.3%)	0	1 (0.3%)	1 (0.2%)	2 (0.2%)
Not reported	13 (4.3%)	22 (7.5%)	11 (3.7%)	33 (5.6%)	46 (5.2%)
Ethnicity, n (%)					
Hispanic or Latino	22 (7.3%)	25 (8.5%)	14 (4.7%)	39 (6.6%)	61 (6.8%)
Not Hispanic or Latino	267 (88.7%)	254 (86.7%)	273 (91.6%)	527 (89.2%)	794 (89.0%)

QUASAR Study					
	Aflibercept 2 mg Q4W n=301 (100%)	Aflibercept 8 mg			Total
		Q8W/3 n=293 (100%)	Q8W/5 n=298 (100%)	Pooled n=591 (100%)	n=892 (100%)
Not reported	12 (4.0%)	14 (4.8%)	11 (3.7%)	25 (4.2%)	37 (4.1%)
Geographic region, n (%)					
Japan	34 (11.3%)	32 (10.9%)	31 (10.4%)	63 (10.7%)	97 (10.9%)
APAC (without Japan)	66 (21.9%)	64 (21.8%)	66 (22.1%)	130 (22.0%)	196 (22.0%)
Europe	113 (37.5%)	111 (37.9%)	114 (38.3%)	225 (38.1%)	338 (37.9%)
America	88 (29.2%)	86 (29.4%)	87 (29.2%)	173 (29.3%)	261 (29.3%)
Age at enrollment (years)					
n	301	293	298	591	892
Mean (SD)	65.9 (11.7)	65.8 (11.5)	65.8 (11.5)	65.8 (11.5)	65.9 (11.6)
Median	67.0	67.0	66.0	67.0	67.0
Q1, Q3	58.0, 74.0	57.0, 75.0	57.0, 74.0	57.0, 75.0	58.0, 74.5
Min, Max	27, 89	23, 95	38, 92	23, 95	23, 95
Age group (years), n (%)					
<55	47 (15.6%)	54 (18.4%)	53 (17.8%)	107 (18.1%)	154 (17.3%)
≥55 to <65	78 (25.9%)	71 (24.2%)	75 (25.2%)	146 (24.7%)	224 (25.1%)
≥65 to <75	103 (34.2%)	92 (31.4%)	96 (32.2%)	188 (31.8%)	291 (32.6%)
≥75	73 (24.3%)	76 (25.9%)	74 (24.8%)	150 (25.4%)	223 (25.0%)
BMI (kg/m2)					
n	300	291	294	585	885
Mean (SD)	27.40 (5.53)	27.55 (5.11)	27.61 (5.02)	27.58 (5.06)	27.52 (5.22)
Median	27.00	27.00	27.10	27.00	27.00
Q1, Q3	23.75, 30.30	24.20, 30.10	24.30, 30.40	24.20, 30.20	24.10, 30.30
Min, Max	14.8, 60.8	16.4, 43.3	14.9, 48.6	14.9, 48.6	14.8, 60.8
Systolic blood pressure (mm Hg)					

QUASAR Study					
	Aflibercept 2 mg Q4W n=301 (100%)	Aflibercept 8 mg			Total
		Q8W/3 n=293 (100%)	Q8W/5 n=298 (100%)	Pooled n=591 (100%)	n=892 (100%)
n	301	293	298	591	892
Mean (SD)	135.38 (11.45)	135.22 (11.74)	134.76 (11.83)	134.99 (11.78)	135.12 (11.66)
Median	135.50	135.50	134.50	135.00	135.00
Q1, Q3	128.00, 143.50	128.00, 143.50	127.50, 141.50	128.00, 142.50	128.00, 143.00
Min, Max	98.0, 160.0	98.0, 158.5	105.5, 177.0	98.0, 177.0	98.0, 177.0
Diastolic blood pressure (mm Hg)					
n	301	293	298	591	892
Mean (SD)	79.36 (7.74)	79.76 (8.16)	79.98 (8.01)	79.87 (8.08)	79.70 (7.97)
Median	80.50	80.00	80.50	80.50	80.50
Q1, Q3	74.50, 85.00	75.00, 85.50	74.50, 86.00	75.00, 86.00	74.75, 85.50
Min, Max	57.0, 96.5	53.0, 96.0	56.0, 99.0	53.0, 99.0	53.0, 99.0
Heart rate (beats/min)					
n	301	293	298	591	892
Mean (SD)	73.1 (10.0)	73.6 (11.1)	73.9 (11.0)	73.8 (11.0)	73.5 (10.7)
Median	72.0	73.0	73.0	73.0	73.0
Q1, Q3	67.0, 80.0	66.0, 80.0	67.0, 80.0	66.0, 80.0	66.0, 80.0
Min, Max	48, 119	48, 115	42, 110	42, 115	42, 119
Prior fellow eye treatment, n (%)					
No	298 (99.0%)	292 (99.7%)	296 (99.3%)	588 (99.5%)	886 (99.3%)
Yes	3 (1.0%)	1 (0.3%)	2 (0.7%)	3 (0.5%)	6 (0.7%)
Aflibercept	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.2%)
Bevacizumab	2 (0.7%)	0	2 (0.7%)	2 (0.3%)	4 (0.4%)
Ranibizumab	1 (0.3%)	0	0	0	1 (0.1%)
Medical history of hypertension, n (%)					

QUASAR Study					
	Aflibercept 2 mg Q4W n=301 (100%)	Aflibercept 8 mg			Total
		Q8W/3 n=293 (100%)	Q8W/5 n=298 (100%)	Pooled n=591 (100%)	n=892 (100%)
No	114 (37.9%)	101 (34.5%)	102 (34.2%)	203 (34.3%)	317 (35.5%)
Yes	187 (62.1%)	192 (65.5%)	196 (65.8%)	388 (65.7%)	575 (64.5%)
Medical history of diabetes, n (%)					
No	240 (79.7%)	240 (81.9%)	246 (82.6%)	486 (82.2%)	726 (81.4%)
Yes	61 (20.3%)	53 (18.1%)	52 (17.4%)	105 (17.8%)	166 (18.6%)
Medical history of cerebrovascular disease, n (%)					
No	282 (93.7%)	268 (91.5%)	283 (95.0%)	551 (93.2%)	833 (93.4%)
Yes	19 (6.3%)	25 (8.5%)	15 (5.0%)	40 (6.8%)	59 (6.6%)
Medical history of ischaemic heart disease, n (%)					
No	273 (90.7%)	271 (92.5%)	275 (92.3%)	546 (92.4%)	819 (91.8%)
Yes	28 (9.3%)	22 (7.5%)	23 (7.7%)	45 (7.6%)	73 (8.2%)
Medical history of renal impairment, n (%)					
Missing	8 (2.7%)	6 (2.0%)	4 (1.3%)	10 (1.7%)	18 (2.0%)
Normal	180 (59.8%)	193 (65.9%)	196 (65.8%)	389 (65.8%)	569 (63.8%)
Mild	94 (31.2%)	75 (25.6%)	76 (25.5%)	151 (25.5%)	245 (27.5%)
Moderate	16 (5.3%)	16 (5.5%)	17 (5.7%)	33 (5.6%)	49 (5.5%)
Severe	3 (1.0%)	3 (1.0%)	5 (1.7%)	8 (1.4%)	11 (1.2%)
Medical history of hepatic impairment, n (%)					
No	288 (95.7%)	278 (94.9%)	287 (96.3%)	565 (95.6%)	853 (95.6%)
Yes	13 (4.3%)	15 (5.1%)	11 (3.7%)	26 (4.4%)	39 (4.4%)
NEI-VFQ-25 total score					
n	301	293	298	591	892
Mean (SD)	78.979 (15.816)	79.395 (15.014)	78.148 (16.027)	78.766 (15.532)	78.838 (15.620)
Median	82.880	82.420	83.095	82.730	82.840

QUASAR Study					
	Aflibercept 2 mg Q4W n=301 (100%)	Aflibercept 8 mg			Total
		Q8W/3 n=293 (100%)	Q8W/5 n=298 (100%)	Pooled n=591 (100%)	n=892 (100%)
Q1, Q3	70.610, 92.010	71.540, 91.210	67.950, 90.420	70.460, 90.870	70.525, 91.060
Min, Max	23.04, 100.00	32.33, 100.00	21.82, 100.00	21.82, 100.00	21.82, 100.00

* Multiple: Participants who reported that they belong to more than one race.

BMI: Body mass index; n: Number of patients; NEI-VFQ-25: National Eye Institute Visual Functioning Questionnaire-25; Q4W: Every 4 weeks; Q8W/3: Every 8 weeks, after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals; SD: Standard deviation

Table 3.Baseline disease characteristics of the study eye

	Aflibercept 2 mg Q4W n=301 (100%)	Aflibercept 8 mg			Total
		Q8W/3 n=293 (100%)	Q8W/5 n=298 (100%)	Pooled n=591 (100%)	n=892 (100%)
RVO Type*, n (%)					
BRVO	149 (49.5%)	159 (54.3%)	159 (53.4%)	318 (53.8%)	467 (52.4%)
CRVO	117 (38.9%)	99 (33.8%)	102 (34.2%)	201 (34.0%)	318 (35.7%)
HRVO	35 (11.6%)	35 (11.9%)	37 (12.4%)	72 (12.2%)	107 (12.0%)
RVO Type (used for stratified randomization)**, n (%)					
BRVO	174 (57.8%)	172 (58.7%)	175 (58.7%)	347 (58.7%)	521 (58.4%)
CRVO/HRVO	127 (42.2%)	121 (41.3%)	123 (41.3%)	244 (41.3%)	371 (41.6%)
BCVA (ETDRS letters score)					
n	301	293	298	591	892
Mean (SD)	54.1 (14.3)	55.2 (13.6)	55.4 (13.4)	55.3 (13.5)	54.9 (13.8)
Median	58.0	57.0	58.0	58.0	58.0
Q1, Q3	45.0, 65.0	47.0, 67.0	49.0, 66.0	48.0, 67.0	47.0, 66.0
Min, Max	24, 73	24, 73	18, 74	18, 74	18, 74
Categorized BCVA (ETDRS letters score), n (%)					
< 60	166 (55.1%)	163 (55.6%)	168 (56.4%)	331 (56.0%)	497 (55.7%)

	Aflibercept 2 mg Q4W n=301 (100%)	Aflibercept 8 mg Q8W/3 n=293 (100%)	Aflibercept 8 mg Q8W/5 n=298 (100%)	Pooled n=591 (100%)	Total n=892 (100%)
≥ 60	135 (44.9%)	130 (44.4%)	130 (43.6%)	260 (44.0%)	395 (44.3%)
Intraocular pressure (mm Hg)					
n	301	293	298	591	892
Mean (SD)	14.6 (3.1)	14.7 (3.1)	14.7 (3.0)	14.7 (3.1)	14.7 (3.1)
Median	14.0	15.0	14.0	15.0	14.5
Q1, Q3	12.0, 17.0	13.0, 17.0	13.0, 17.0	13.0, 17.0	13.0, 17.0
Min, Max	6, 24	7, 24	7, 26	7, 26	6, 26
Central subfield thickness (CST) (um)					
n	300	293	298	591	891
Mean (SD)	651.0 (240.0)	626.1 (230.2)	609.2 (213.3)	617.6 (221.8)	628.8 (228.5)
Median	603.5	575.0	569.0	574.0	581.0
Q1, Q3	474.5, 766.0	457.0, 754.0	451.0, 745.0	452.0, 747.0	459.0, 754.0
Min, Max	302, 1601	272, 1499	268, 1424	268, 1499	268, 1601
Categorized CST					
Missing	1 (0.3%)	0	0	0	1 (0.1%)
≤ Observed Median (581 um)	141 (46.8%)	148 (50.5%)	157 (52.7%)	305 (51.6%)	446 (50.0%)
> Observed Median (581 um)	159 (52.8%)	145 (49.5%)	141 (47.3%)	286 (48.4%)	445 (49.9%)
Presence of perifoveal and parafoveal ischemia by FA					
Missing	23 (7.6%)	14 (4.8%)	22 (7.4%)	36 (6.1%)	59 (6.6%)
No	72 (23.9%)	56 (19.1%)	62 (20.8%)	118 (20.0%)	190 (21.3%)
Undetermined	28 (9.3%)	24 (8.2%)	29 (9.7%)	53 (9.0%)	81 (9.1%)
Yes	178 (59.1%)	199 (67.9%)	185 (62.1%)	384 (65.0%)	562 (63.0%)
Total area of macular ischemia (not considering the FAZ) by FA (mm2)					
n	257	247	250	497	754

	Aflibercept 2 mg Q4W n=301 (100%)	Aflibercept 8 mg			Total n=892 (100%)
		Q8W/3 n=293 (100%)	Q8W/5 n=298 (100%)	Pooled n=591 (100%)	
Mean (SD)	4.204 (4.804)	4.681 (4.831)	4.643 (4.909)	4.662 (4.866)	4.506 (4.847)
Median	2.900	3.910	3.255	3.810	3.300
Q1, Q3	0.000, 7.750	0.000, 7.730	0.000, 8.080	0.000, 7.920	0.000, 7.920
Min, Max	0.00, 28.08	0.00, 26.86	0.00, 24.20	0.00, 26.86	0.00, 28.08
Presence of retinal areas of non-perfusion outside the macula by FA					
Missing	13 (4.3%)	11 (3.8%)	13 (4.4%)	24 (4.1%)	37 (4.1%)
No	72 (23.9%)	67 (22.9%)	64 (21.5%)	131 (22.2%)	203 (22.8%)
Undetermined	27 (9.0%)	18 (6.1%)	28 (9.4%)	46 (7.8%)	73 (8.2%)
Yes	189 (62.8%)	197 (67.2%)	193 (64.8%)	390 (66.0%)	579 (64.9%)

* RVO type based on reading center assessment (investigator assessment is used for participants with missing reading center data).

** RVO type based on investigator assessment; used for strata assignment at randomization via the IxRS system.

BCVA: Best corrected visual acuity; BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion; CST: Central subfield thickness; ETDRS: Early treatment diabetic retinopathy study; FA: Fluorescein angiography assessment; FAZ: Foveal avascular zone; HRVO: Hemi-retinal vein occlusion; n: Number of patients; Q4W: Every 4 weeks; Q8W/3: Every 8 weeks, after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals; RVO: Retinal vein occlusion; SD: Standard deviation

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

5.2.1.1 Patient disposition

The disposition of patients in QUASAR is described in Table 4. There were 1282 enrolled patients, of whom 388 did not complete screening. Of the enrolled patients, 894 were randomised, and 892 patients were treated (full analysis set (FAS) and safety analysis set (SAF)). Of these, 838 patients completed the study treatment phase through week 36.

Table 4. Patient disposition through week 36

	Aflibercept 2 mg Q4W	Aflibercept 8 mg			Total
		Q8W/3	Q8W/5	Pooled	
Enrolled	-	-	-	-	1282 (100.0%)
Did not complete screening	-	-	-	-	388 (30.3%)
Randomized to intervention	302 (100.0%)	294 (100.0%)	298 (100.0%)	592 (100.0%)	894 (100.0%)
Study intervention never administered	1 (0.3%)	1 (0.3%)	0	1 (0.2%)	2 (0.2%)
Treated	301 (99.7%)	293 (99.7%)	298 (100.0%)	591 (99.8%)	892 (99.8%)
Treatment phase through week 36					
Started	301 (99.7%)	293 (99.7%)	298 (100.0%)	591 (99.8%)	892 (99.8%)
Completed treatment phase through week 36	287 (95.0%)	278 (94.6%)	273 (91.6%)	551 (93.1%)	838 (93.7%)
Did not complete treatment phase through week 36	14 (4.6%)	15 (5.1%)	25 (8.4%)	40 (6.8%)	54 (6.0%)
Primary reason					
Adverse event	2 (0.7%)	0	2 (0.7%)	2 (0.3%)	4 (0.4%)
Death	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)	7 (0.8%)
Logistical problem	0	1 (0.3%)	0	1 (0.2%)	1 (0.1%)
Lost to follow-up	2 (0.7%)	3 (1.0%)	3 (1.0%)	6 (1.0%)	8 (0.9%)
Physician decision	0	1 (0.3%)	0	1 (0.2%)	1 (0.1%)
Protocol deviation	0	0	1 (0.3%)	1 (0.2%)	1 (0.1%)
Withdrawal by subject	8 (2.6%)	8 (2.7%)	16 (5.4%)	24 (4.1%)	32 (3.6%)
Follow-up phase					
Started follow-up phase prior to week 36	14 (4.6%)	15 (5.1%)	25 (8.4%)	40 (6.8%)	54 (6.0%)
Completed follow-up phase through week 36	0	0	0	0	0
Unknown if completed follow-up phase through week 36	0	2 (0.7%)	2 (0.7%)	4 (0.7%)	4 (0.4%)
Did not complete follow-up phase through week 36	14 (4.6%)	13 (4.4%)	23 (7.7%)	36 (6.1%)	50 (5.6%)
Primary reason					
Adverse event	2 (0.7%)	0	1 (0.3%)	1 (0.2%)	3 (0.3%)
Death	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)	7 (0.8%)
Lost to follow-up	2 (0.7%)	2 (0.7%)	2 (0.7%)	4 (0.7%)	6 (0.7%)
Physician decision	0	1 (0.3%)	0	1 (0.2%)	1 (0.1%)

	Aflibercept 2 mg Q4W	Aflibercept 8 mg			Total
		Q8W/3	Q8W/5	Pooled	
Protocol deviation	0	0	1 (0.3%)	1 (0.2%)	1 (0.1%)
Withdrawal by subject	8 (2.6%)	8 (2.7%)	16 (5.4%)	24 (4.1%)	32 (3.6%)

The number of participants enrolled is the number of participants who signed informed consent. In rescreening, rescreened participants are counted once, along with their final enrolment.

Definition of completed treatment phase through week 36: Did not discontinue study intervention prior to week 36 visit and reached the week 36 visit (either visit performed or confirmed not done).

Definition of completed follow-up phase through week 36: The end of treatment was prior to week 36, but the study discontinuation date was at week 36 or later.

The follow-up phase started after the date of treatment discontinuation for the participant.

Q4W: Every 4 weeks, Q8W/3: Every 8 weeks; after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals

5.2.2 Clinical efficacy from QUASAR: Results at 36 weeks

5.2.2.1 Primary endpoint: Change from baseline in BCVA measured by the ETDRS letter score at week 36

The QUASAR study found that aflibercept 8 mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals was non-inferior to aflibercept 2 mg injected every 4 weeks in terms of least-squares (LS) mean improvement from BCVA as measured by ETDRS letter score at week 36 (Table 5). The primary analysis of the change from baseline in BCVA resulted in LS mean changes from baseline to week 36 of 17.5 letters in the aflibercept 2 mg Q4W group compared with 17.4 letters in the aflibercept 8 mg Q8W/3 group ($p<0.0001$ for non-inferiority versus aflibercept 2 mg Q4W group) and 18.3 letters in the aflibercept 8 mg Q8W/5 group ($p<0.0001$ for non-inferiority versus aflibercept 2 mg Q4W group).

The primary analysis results in the FAS population are supported by the overall population and all subgroup and sensitivity analyses; for more details, see the QUASAR Clinical Study Report (week 36).

Table 5. Change from baseline in BCVA measured by the ETDRS letter score at week 36, MMRM

Full analysis set	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
Number of participants with week 36 data: included/excluded due to ICE	264/17	260/12	248/18
Baseline mean*	54.1	55.2	55.4
Arithmetic mean (SD) change from baseline*	17.8 (13.1)	17.0 (11.8)	19.1 (11.2)
LS mean (SE) change from baseline	17.5 (0.7)	17.4 (0.7)	18.3 (0.6)
DF	-	558.4	543.1
Contrast**	-	Q8W/3 - Q4W	Q8W/5 - Q4W
t-value	-	3.94	4.92

p-value of one-sided test for non-inferiority at a margin of 4 letters	-	<0.0001	<0.0001
p-value of one-sided test for superiority	-	0.5262	0.2067
Estimate for contrast and two-sided 95% CI* **	-	-0.1 (-2.0, 1.9)	0.8 (-1.1, 2.7)

A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors, and terms for the interaction between baseline BCVA and visit and treatment and visit. Covariance structure used: unstructured covariance structure. Intercurrent events were handled according to primary estimand strategy.

* Based on observed cases, excluding data after ICE.

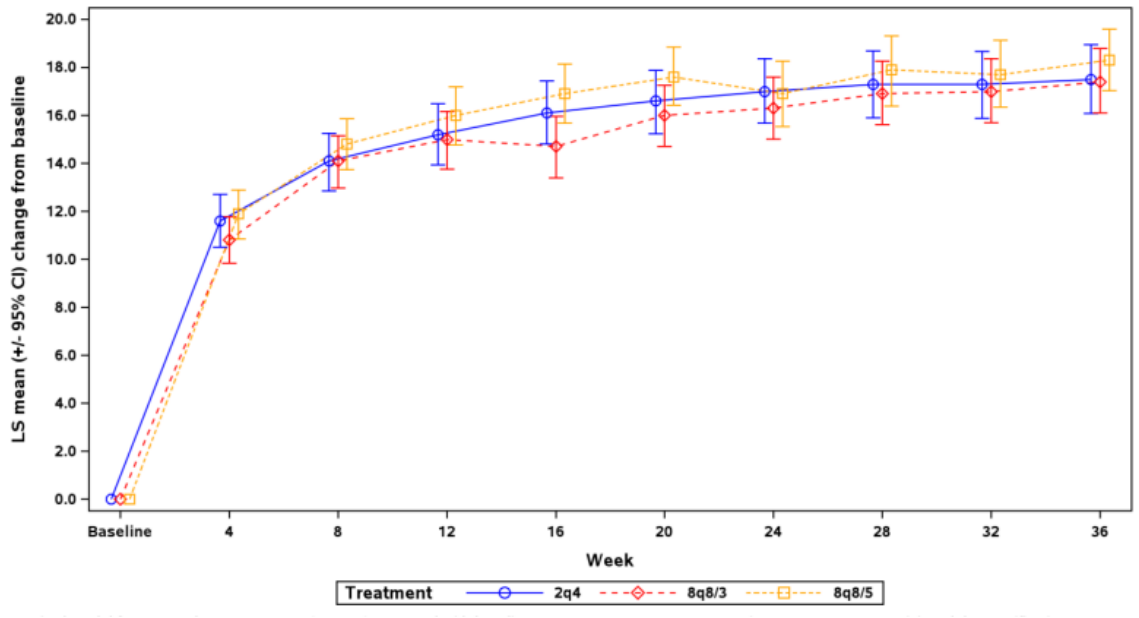
** The contrast also includes the interaction term for treatment x visit (at week 36).

*** The estimate based on the MMRM was computed for the differences of Q8W/3 minus Q4W and Q8W/5 minus Q4W, respectively, with two-sided 95% CIs.

BCVA: Best corrected visual acuity; BL: Baseline; CI: Confidence interval; DF: Degrees of freedom; ETDRS: Early Treatment Diabetic Retinopathy Study; ICE: Intercurrent event; LS: Least squares; Q4W: Every 4 weeks; Q8W/3: Every 8 weeks, after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; SD: Standard deviation; SE: Standard error

Least-squares mean changes from baseline in BCVA measured by the ETDRS letter score by visit were similar across aflibercept 2 mg Q4W, aflibercept 8 mg Q8W/3, and aflibercept 8 mg Q8W/5 treatment groups, demonstrating the robustness of results on the primary endpoint (Figure 2).

Figure 2. Least-squares mean change from baseline in BCVA measured by the ETDRS letter score by visit, MMRM (full analysis set)



MMRM was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors, and terms for the interaction between baseline BCVA and visit and treatment and visit. Covariance structure used: unstructured covariance structure.

Intercurrent events were handled according to the primary estimand strategy.

2q4: Aflibercept 2mg administered every 4 weeks; 8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals; 8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals; BCVA: Best corrected visual acuity; CI: Confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; LS: Least squares; MMRM: Mixed model for repeated measurements

5.2.2.2 Secondary endpoints

5.2.2.3 Number of active injections from baseline to week 36

The QUASAR study revealed that both the aflibercept 8 mg Q8W/3 and Q8W/5 regimens resulted in fewer active injections compared to the aflibercept 2 mg Q4W regimen over the 36 weeks. The primary analysis resulted in LS mean values of 6.1 injections in the aflibercept 8 mg Q8W/3 group, 6.9 injections in the aflibercept 8 mg Q8W/5 group, and 8.8 injections in the aflibercept 2 mg Q4W group. The comparison between aflibercept 8 mg Q8W/3 and aflibercept 2 mg Q4W demonstrated a significant difference with a p-value of <0.0001, as did the comparison between aflibercept 8 mg Q8W/5 and aflibercept 2 mg Q4W, p-value of <0.0001 (Table 6).

Similar results were obtained in the analysis in subgroups by the RVO type (BRVO and CRVO/HRVO); for more details, see the QUASAR Clinical Study Report (week 36).

Table 6. Number of active injections from baseline to Week 36, Main Analysis

Full analysis set	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
LS mean (SE) number of active injections*	8.8 (0.0)	6.1 (0.0)	6.9 (0.0)
Contrast	-	Q8W/3 - Q4W	Q8W/5 - Q4W
Estimate for contrast and two-sided 95% CI*	-	-2.7 (-2.8, -2.6)	-1.8 (-1.9, -1.7)
p-value**	-	<0.0001	<0.0001

Missing endpoint values were imputed using a multiple imputation approach.

A non-parametric rank analysis of covariance (ANCOVA) was used on each imputed data, adjusting for baseline BCVA, baseline CST, and the stratification variables (geographic region [Japan + APAC vs. Europe vs. America], BCVA score [<60 vs. ≥60], and RVO type [CRVO/HRVO vs. BRVO]) and results were combined using Rubin's rule.

* Based on Rubin's rule application after fitting a linear regression model adjusted for the same covariates as the non-parametric rank ANCOVA on each imputed dataset.

** p-value based on the non-parametric rank ANCOVA applied to each imputed dataset and combined using Rubin's rule.

CI: Confidence interval; LS: Least square; Q4W: Every 4 weeks; Q8W/3: Every 8 weeks, after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; SE: Standard error

5.2.2.4 Exposure to intervention in the study eye through week 36

In the QUASAR study, most patients used Q8W dosing intervals or longer in both aflibercept 8 mg Q8W/3 and Q8W/5 study arms through 36 weeks. Q8W was the last intended dosing interval in 93.4% of participants from the aflibercept 8 mg Q8W/5 study arm compared with 75.6% of participants from the aflibercept 2 mg Q4W study arm. Most participants from the aflibercept 8 mg Q8W/3 (69.1%) used Q12W dosing intervals as the last intended dosing interval, and 24.8% used Q8W, indicating extended dosing intervals early in the patient treatment (Table 7).

Table 7. Exposure to intervention in the study eye through week 36 (safety analysis set, only participants considered as completers for week 36)

Safety analysis set	Aflibercept 2 mg Q4W n=287	Aflibercept 8 mg Q8W/3 n=278	Aflibercept 8 mg Q8W/5 n=273
Participants with Q8W or longer dosing interval through Week 36 *	-	246 (88.5%)	255 (93.4%)
Participants with Q4W as the last intended dosing interval **	70 (24.4%)	17 (6.1%)	18 (6.6%)
Participants with Q8W as the last intended dosing interval **	217 (75.6%)	69 (24.8%)	255 (93.4%)
Participants with Q12W as the last intended dosing interval *	-	192 (69.1%)	-

* All participants on Q8W interval for whom it was not planned to have their interval shortened (according to DRM criteria until W32) prior to Week 36.

** Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 36.

5.2.2.5 Number of participants gaining at least 15 letters in BCVA from baseline at week 36

The proportions of participants gaining ≥15 letters in BCVA from baseline at week 36 were similar across the aflibercept 2 mg Q4W and aflibercept 8 mg Q8W/3, and numerically slightly higher for aflibercept 8 mg Q8W/5 treatment groups (59.8%, 58.8%, and 64.9%, respectively) (Table 8).

5.2.2.6 Number of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at week 36

The proportions of participants achieving an ETDRS letter score of ≥69 (approximately 20/40 Snellen equivalent) at week 36 using observed cases were numerically higher across aflibercept 8 mg Q8W/3 and aflibercept 8 mg Q8W/5 as compared to the aflibercept 2 mg Q4W. In the aflibercept 2 mg Q4W treatment group, 67.8% of patients achieved an ETDRS score of ≥69 at week 36. Among participants from the aflibercept 8 mg Q8W/3 and Q8W/5 treatment groups, the proportions of patients who achieved an ETDRS score of ≥69 were 72.7% and 76.2%, respectively (Table 8).

5.2.2.7 Participants having no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the center subfield at week 36

The proportion of patients with no IRF and no SRF in the center subfield at 36 weeks across the aflibercept 8 mg Q8W/3 and Q8W/5 treatment groups was 81.2% and 81.8%, respectively. Aflibercept 2 mg Q4W had a minimally higher proportion (83.7%) of participants with no IRF and no SRF at week 36 (Table 8).

Table 8. The proportion of participants achieving some visual and anatomic measures of response at week 36, observed cases (OC) excluding values after ICE (full analysis set)

Visual and anatomic measures Num/Den (%)	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
Participants who gained at least 15 letters	158/264 (59.8%)	153/260 (58.8%)	161/248 (64.9%)
Participants who achieved a letter score of at least 69	179/264 (67.8%)	189/260 (72.7%)	189/248 (76.2%)
Participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF)	221/264 (83.7%)	211/260 (81.2%)	202/247 (81.8%)

OC meant all observed cases, excluding values after intercurrent event (ICE).

Missing cases will not be included in the denominator when calculating proportions.

IRF: Intraretinal fluid; Q4W: Every 4 weeks; Q8W/3: Every 8 weeks, after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; SRF: Subretinal fluid

5.2.2.8 Change from baseline in CST at week 36

The mean CST at baseline differs numerically across the aflibercept 2 mg Q4W and aflibercept 8 mg (Q8W/3 and Q8W/5) treatment groups. The arithmetic mean change in CST from baseline at week 36 showed a reduction in all treatment groups. The aflibercept 2 mg Q4W group had a mean decrease of -397.3 µm, the aflibercept 8 mg Q8W/3 group showed a mean decrease of -365.9 µm, while the aflibercept 8 mg Q8W/5 group had a mean change of -351.0 µm. The LS mean changes from baseline at week 36 were very similar across the three groups. The LS mean change for the aflibercept 2 mg Q4W group was -370.8 µm, for aflibercept 8 mg Q8W/3 it was -370.9 µm, and -369.5 µm for aflibercept 8 mg Q8W/5, with no statistically significant differences between aflibercept 8 mg (both Q8W/3 and Q8W/5) and aflibercept 2 mg (p=0.9804 and 0.7863, respectively) (Table 9).

Table 9. Change from baseline in CST (µm) at week 36, MMRM (full analysis set)

Full analysis set	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
Number of patients with week 36 data, included/excluded due to ICE	262/17	260/11	247/18
Baseline mean*	651.0	626.1	609.2
Arithmetic mean (SD) change from baseline*	-397.3 (257.7)	-365.9 (239.9)	-351.0 (225.4)
LS mean (SE) change from baseline	-370.8 (3.9)	-370.9 (3.1)	-369.5 (2.3)
DF	-	537.1	450.3
Contrast**	-	Q8W/3 – Q4W	Q8W/5 – Q4W
t-value	-	-0.02	0.27
p-value for the two-sided test	-	0.9804	0.7863
Estimate for contrast and two-sided 95% CI***	-	-0.1 (-10.0, 9.8)	1.2 (-7.7, 10.2)

A mixed model for repeated measurements (MMRM) was used with baseline CST measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs. ≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors, and terms for the interaction between baseline CST and visit and treatment and visit. Covariance structure used: unstructured covariance structure. Intercurrent events were handled according to the primary estimand strategy.

* Based on observed cases, excluding data after ICE.

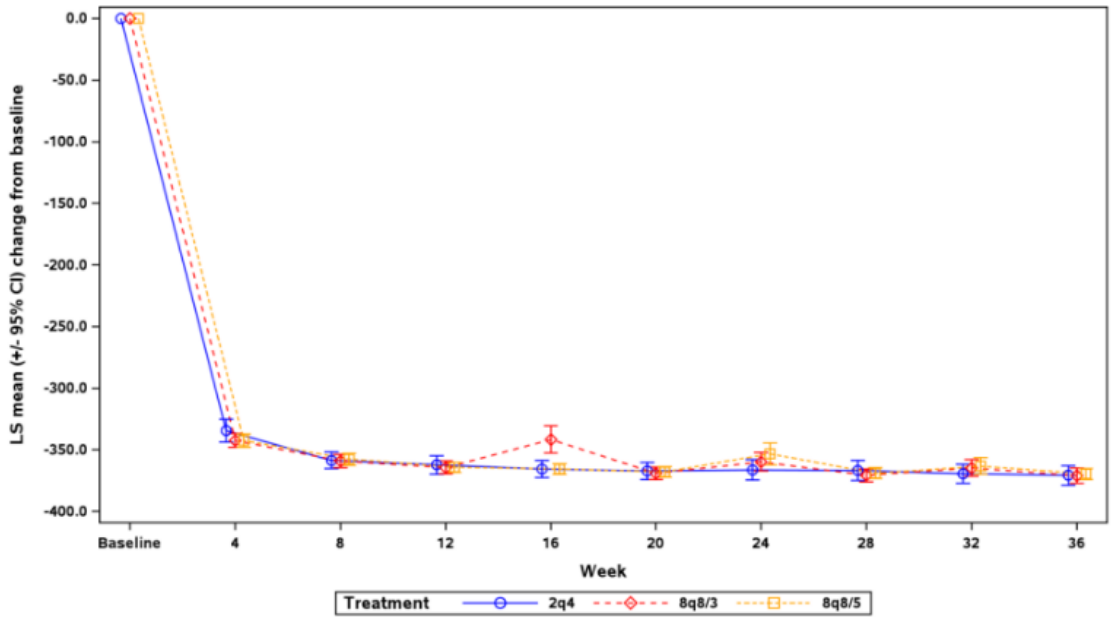
** The contrast also includes the interaction term for treatment x visit.

*** The estimate based on the MMRM, was computed for the differences of Q8W/3 minus Q4W and Q8W/5 minus Q4W.

BL: Baseline; CI: Confidence interval; CST: Central subfield thickness; DF: Degrees of freedom; ICE: Intercurrent event; LS: Least squares; Q4W: Every 4 weeks, Q8W/3: Every 8 weeks; after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; SD: Standard deviation; SE: Standard error

Least-squares mean changes from baseline in CST by visit were similar across aflibercept 2 mg Q4W, aflibercept 8 mg Q8W/3, and aflibercept 8 mg Q8W/5 treatment groups. The CST fluctuation at the 16-week timepoint for the aflibercept 8 mg Q8W/3 arm was minimal and not considered clinically meaningful (Figure 3).

Figure 3. Least-squares mean change from baseline in CST (µm) by visit, MMRM (full analysis set)



MMRM was used with baseline CST measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors, and terms for the interaction between baseline CST and visit and treatment and visit. Covariance structure used: unstructured covariance structure.

Intercurrent events were handled according to the primary estimand strategy.

2q4: Aflibercept 2mg administered every 4 weeks; 8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals; 8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals; CI: Confidence interval; CST: Central subfield thickness; LS: Least squares; MMRM: Mixed model for repeated measurements

5.2.2.9 Change from baseline in NEI VFQ 25 total score at week 36

The QUASAR study demonstrates that aflibercept 8 mg treatment groups provide comparable efficacy to aflibercept 2 mg in terms of improvement in vision-related QoL as measured by the NEI VFQ-25 questionnaire at week 36. The mean values of the NEI VFQ-25 total score at baseline were similar across the aflibercept 2 mg and aflibercept 8 mg treatment groups (Q8W/3 and Q8W/5) and ranged from 78.15 to 79.39. The LS mean changes in the NEI VFQ-25 total score at week 36 were 5.91 in the aflibercept 8 mg Q8W/3 group, 6.92 in the aflibercept 8 mg Q8W/5, and 6.27 in the aflibercept 2 mg Q4W group, with no statistically significant differences between aflibercept 8 mg (both Q8W/3 and Q8W/5) and aflibercept 2 mg (p=0.6869 and 0.4792, respectively) (Table 10).

Table 10. Change from baseline in NEI-VFQ-25 total score at week 36, ANCOVA (full analysis set)

Full analysis set	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
Number of patients with week 36 data, included/excluded due to ICE	263/17	259/12	249/17
Baseline mean*	78.98	79.39	78.15
Arithmetic mean (SD) change from baseline**	6.00 (13.03)	5.65 (11.37)	7.32 (12.50)
LS mean (SE) change from baseline	6.27 (0.67)	5.91 (0.61)	6.92 (0.63)
Contrast	-	Q8W/3 – Q4W	Q8W/5 – Q4W
DF	-	512	507
t-value	-	-0.40	0.71
p-value for the two-sided test	-	0.6869	0.4792
Estimate for Contrast and two-sided 95% CI***	-	-0.36 (-2.1,1.40)	0.65 (-1.2,2.45)

An analysis of covariance (ANCOVA) was used with baseline NEI-VFQ-25 total score measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs. ≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors.

Data after the occurrence of an ICE was excluded in line with the sensitivity estimand.

* Based on observed assessments.

** Based on observed assessment, excluding data after ICEs.

*** The estimate based on the ANCOVA model was computed for the differences of Q8W/3 minus Q4W and Q8W/5 minus Q4W, respectively.

BL: Baseline; CI: Confidence interval; DF: Degrees of freedom; ICE: Intercurrent event; LS: Least squares; Q4W: Every 4 weeks, Q8W/3: Every 8 weeks after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; SD: Standard deviation; SE: Standard error

5.2.2.10 Proportion of subjects who lost less than 15 letters in BCVA from baseline by visit at week 36

Table 11. Proportion of subjects who lost less than 15 letters in BCVA from baseline to week 36

Full analysis set - week 36	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
Subjects who lost < 15 letters Num/Den (%)	293/301 (97.3%)	287/293 (98.0%)	291/298 (97.7%)

(a) CI=Miettinen-Nurminen confidence interval. (b) CI=Wald confidence interval.
Intercurrent events will be handled according to sensitivity estimand strategy for continuous endpoints as described in Table 4-2 in Section 4.2.2.1 of the SAP.
LOCF (last observation carried forward): last available observed value prior to ICE will be used to impute missing data. 2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals. 8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

5.2.3 Clinical efficacy from QUASAR: Results at 64 weeks

Efficacy of aflibercept 8 mg for the treatment of RVO, observed at week 36 in the QUASAR trial, was confirmed at week 64. The following sections provide an overview of the data, more details can be found in the Clinical study report.

5.2.3.1 Primary endpoint: Change from baseline in BCVA measured by the ETDRS letter score at week 64

The non-inferior vision gains achieved by aflibercept 8 mg Q8/3 and Q8/5 versus aflibercept 2 mg Q4W have been maintained through week 64 as shown in Table 12. The change from baseline BCVA resulted in LS mean changes of 17.8 letters and 18.1 letters in the aflibercept 8 mg Q8W/3 and Q8W/5 groups, respectively, compared to the 17.3 letters achieved in the 2 mg Q4W group (p<0.0001 for non-inferiority in both comparisons). Similar results were obtained for the BRVO and CRVO/HRVO subgroups.

Table 12. Change from baseline in BCVA measured by the ETDRS letter score at week 64, MMRM

Full analysis set	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
Number of participants with week 64 data: included/excluded due to ICE	255/15	253/15	240/16
Baseline mean*	54.1	55.2	55.4
Arithmetic mean (SD) change from baseline*	17.4 (14.6)	17.3 (12.7)	19.2 (13.0)
LS mean (standard error) change from baseline	17.3 (0.8)	17.8 (0.7)	18.1 (0.8)
DF	-	555.8	521.8
Contrast**	-	Q8W/3 - Q4W	Q8W/5 - Q4W
t-value	-	4.14	4.21
p-value of one-sided test for non-inferiority at a margin of 4 letters	-	<.0001	<.0001
p-value of one-sided test for superiority	-	0.3198	0.2597
Estimate for contrast and two-sided 95% CI***	-	0.5 (-1.6, 2.7)	0.7 (-1.5, 2.9)

A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors, and terms for the interaction between baseline BCVA and visit and treatment and visit. Covariance structure used: unstructured covariance structure. Intercurrent events were handled according to primary estimand strategy.

* Based on observed cases, excluding data after ICE.

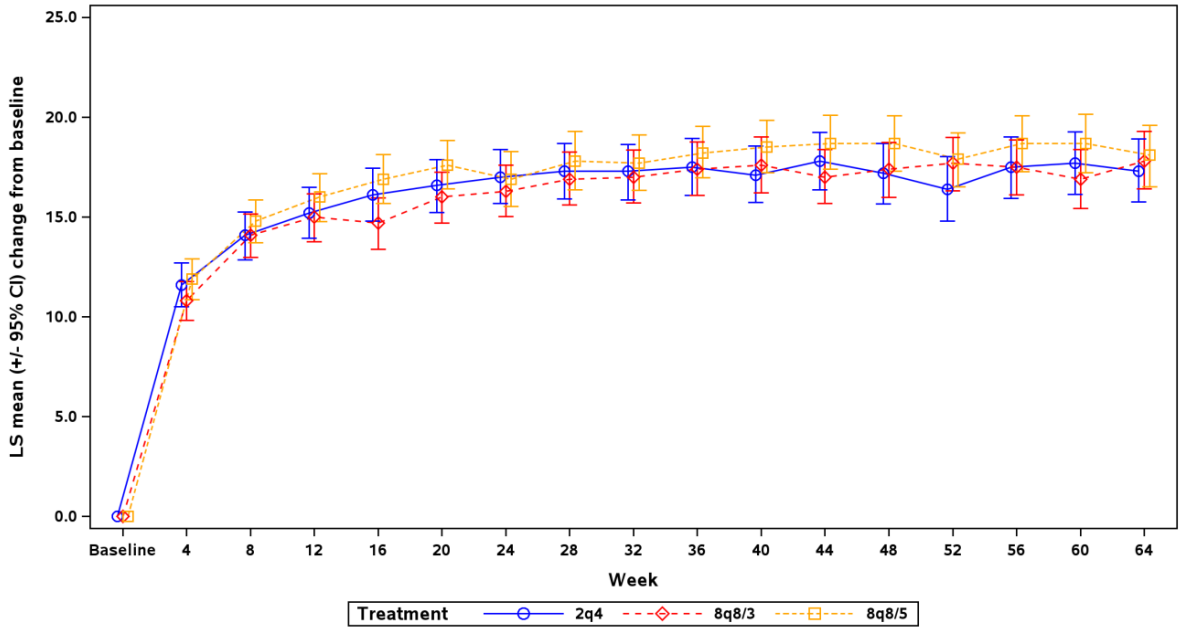
** The contrast also includes the interaction term for treatment x visit (at week 64).

*** The estimate based on the MMRM was computed for the differences of Q8W/3 minus Q4W and Q8W/5 minus Q4W, respectively, with two-sided 95% CIs.

BCVA: Best corrected visual acuity; BL: Baseline; CI: Confidence interval; DF: Degrees of freedom; ETDRS: Early Treatment Diabetic Retinopathy Study; ICE: Intercurrent event; LS: Least squares; Q4W: Every 4 weeks; Q8W/3: Every 8 weeks, after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; SD: Standard deviation

Least-squares mean changes from baseline in BCVA measured by the ETDRS letter score by visit were similar across aflibercept 2 mg Q4W, aflibercept 8 mg Q8W/3, and aflibercept 8 mg Q8W/5 treatment groups, demonstrating the robustness of results on the primary endpoint (Figure 26).

Figure 4. Least-squares mean change from baseline in BCVA measured by the ETDRS letter score by visit, MMRM (full analysis set)



MMRM was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors, and terms for the interaction between baseline BCVA and visit and treatment and visit. Covariance structure used: unstructured covariance structure.

Intercurrent events were handled according to the primary estimand strategy.

2q4: Aflibercept 2mg administered every 4 weeks; 8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals; 8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals; BCVA: Best corrected visual acuity; CI: Confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; LS: Least squares; MMRM: Mixed model for repeated measurements

5.2.3.2 Key secondary endpoint: Number of active injections at week 64

The number of active injections from baseline was assessed as key secondary endpoint at week 64. The analysis of the key secondary endpoint is included in the testing hierarchy and is thus considered confirmatory.

A statistically significant lower LS mean number of active injections were administered to the aflibercept 8 mg Q8W/3 and Q8W/5 groups (8.5 and 9.5, respectively) compared to the aflibercept 2 mg Q4W group (11.7 active injections). The estimated difference in the LS mean number of active injections from baseline to Week 64 suggests a clinically meaningful reduction for both 8 mg groups in comparison with the 2 mg treatment group (Table 13).

Table 13. Number of active injections from baseline to Week 64, Main Analysis

Full analysis set	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
LS mean (standard error) number of active injections*	11.7 (0.1)	8.5 (0.1)	9.5 (0.1)
Contrast	-	Q8W/3 - Q4W	Q8W/5 - Q4W
Estimate for contrast and two-sided 95% CI*	-	-3.2 (-3.5, -3.0)	-2.2 (-2.4, -2.0)
p-value**	-	<0.0001	<0.0001

Missing endpoint values were imputed using a multiple imputation approach as described in SAP Section 4.3.1.2 in W36 CSR Section 10.1.9.

A non-parametric rank ANCOVA was used on each imputed dataset, adjusting for baseline BCVA, baseline CST, and the stratification variables (geographic region [Japan + APAC vs. Europe vs. America], BCVA score [<60 vs. ≥60], and RVO type [CRVO/HRVO vs. BRVO]) and results were combined using Rubin's rule.

ICEs were handled according to secondary estimand strategy as described in Table 4-6 of the SAP Section 4.3.1.3 in W36 CSR Section 10.1.9.

(a) Based on the application of Rubin's rule after fitting a linear regression model adjusted for the same covariates as the non-parametric rank ANCOVA on each imputed dataset.

(b) p-value based on the non-parametric rank ANCOVA applied to each imputed dataset and combined using Rubin's rule.

CI: Confidence interval; LS: Least square; Q4W: Every 4 weeks; Q8W/3: Every 8 weeks, after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals

A supportive exploratory subgroup analysis for BRVO and CRVO/HRVO for the key secondary efficacy variable, the number of active injections, was performed. The analysis showed no substantial differences across the different RVO types. In both RVO types the results observed were consistent with those in the pooled RVO group.

5.2.3.3 Further secondary endpoints

5.2.3.4 Exposure to intervention in the study eye through week 64

The last *completed* interval and last *intended* interval at week 64 were both assessed as secondary endpoints. In the aflibercept 8 mg treatment groups, >88% of patients maintained the initial Q8W dosing or was further extended through week 64 (88.1% in the Q8W/3 and 91.0% in the Q8W/5 group), without ever shortening their intervals according to the DRM criteria.

For aflibercept 8mg Q8W/3 and Q8W/5, more than half of the patients' last assigned treatment intervals were higher than Q16W (64.3% for Q8W/3 and 62.1% for Q8W/5). (Figure 5)

Table 14 below details the last *completed* and last *intended* treatment intervals at the end of the QUASAR study.

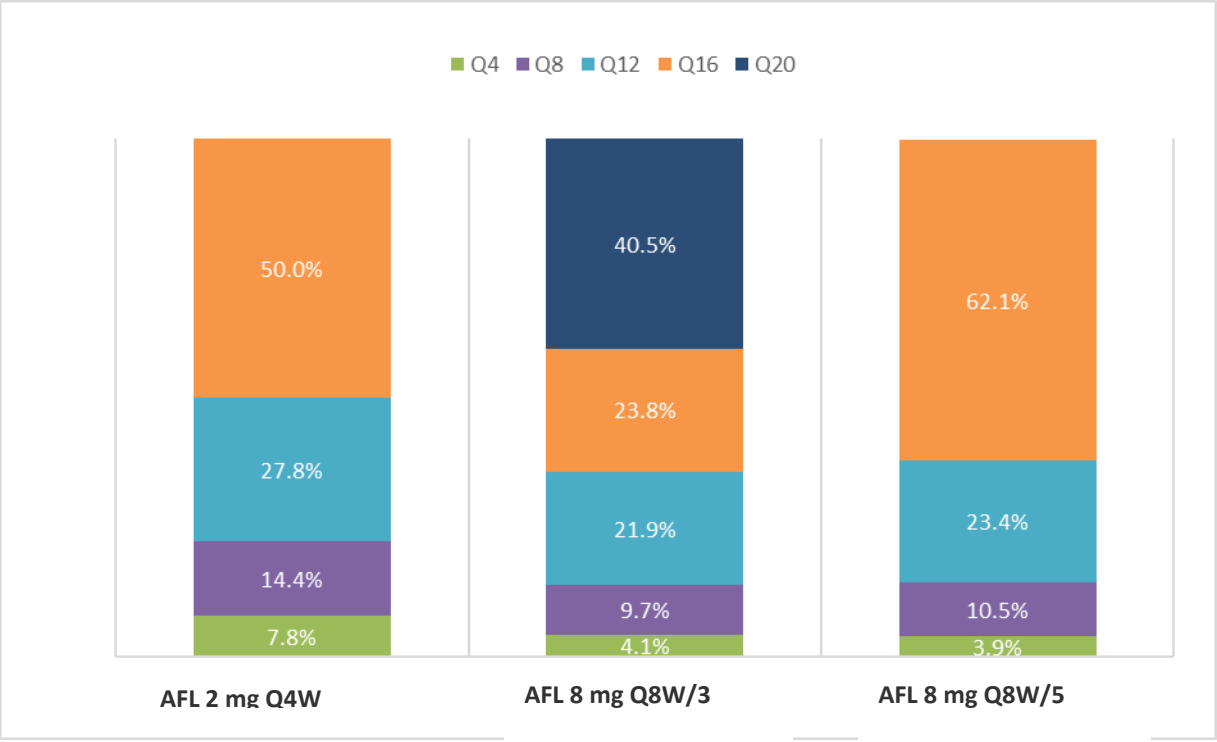
Table 14. Treatment exposure through week 64

Safety analysis set	Aflibercept 2 mg Q4W n=270	Aflibercept 8 mg Q8W/3 n=269	Aflibercept 8 mg Q8W/5 n=256
Last *completed* dosing interval (% of patients)			
Q4W	13.0%	4.8%	3.5%
Q8W	19.3%	13.8%	18.0%
Q12W	67.8%	25.3%	78.5%
Q16W	-	56.1%	-
Last *intended* dosing interval (% of patients)*			
Q4W	7.8%	4.1%	3.9%
Q8W	14.4%	9.7%	10.5%
Q12W	27.8%	21.9%	23.4%
Q16W	50.0%	23.8%	62.1%
Q20W	-	40.5%	-

Duration (weeks) = [(date of last study intervention prior to Week 64) - (date of first study intervention) +28]/7; 28 days were added because of the minimum 4-week dosing interval in the study.
Only participants that did not discontinue study intervention prior to Week 64 are included.
*Based on DRM criteria assessed at the last visit with active injection before Week 64.

Q12W: Every 12 weeks; Q4W: Every 4 weeks; Q8W: Every 8 weeks; Q8W/3: Every 8 weeks, after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals

Figure 5. Last assigned treatment intervals at week 64



5.2.3.5 Change from baseline CST at week 64

Similar decrease from baseline was observed in all treatment groups at Week 64, (-353.7, -361.1 and -353.3 µm in AFL 2 mg Q4W, AFL 8 mg Q8W/3 and Q8W/5 groups, respectively). The estimated difference in LS mean changes in CST from baseline at Week 64 were low, i.e. -7.4 µm for AFL 8 mg Q8W/3 vs. 2 mg Q4W and of 0.5 µm for AFL 8 mg Q8W/5 vs. 2 mg Q4W. (Table 15)

The LS mean decreases from baseline in CST over time were similar across all groups with generally minor numerical differences that were not considered clinically meaningful.

Table 15. Change from baseline CST at week 64

Full analysis set	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
Number of patients with week 36 data, included/excluded due to ICE	252/15	253/14	240/15
Baseline mean*	651.0	626.1	609.2
Arithmetic mean (SD) change from baseline*	-373.0 (252.1)	-355.5 (239.5)	-339.8 (229.6)
LS mean (standard error) change from baseline	-353.7 (5.2)	-361.1 (4.3)	-353.3 (4.1)
DF		493.8	484.3
Contrast**		Q8W/3 – Q4W	Q8W/5 – Q4W
t-value		-1.09	0.07
p-value for the two-sided test		0.2779	0.9455
Estimate for contrast and two-sided 95% CI***		-7.4 (-20.7, 5.9)	0.5 (-12.6, 13.5)

A mixed model for repeated measurements (MMRM) was used with baseline CST measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs. ≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors, and terms for the interaction between baseline CST and visit and treatment and visit. Covariance structure used: unstructured covariance structure. Intercurrent events were handled according to the primary estimand strategy.

* Based on observed cases, excluding data after ICE.

** The contrast also includes the interaction term for treatment x visit.

*** The estimate based on the MMRM, was computed for the differences of Q8W/3 minus Q4W and Q8W/5 minus Q4W.

BL: Baseline; CI: Confidence interval; CST: Central subfield thickness; DF: Degrees of freedom; ICE: Intercurrent event; LS: Least squares; Q4W: Every 4 weeks, Q8W/3: Every 8 weeks; after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; SD: Standard deviation

5.2.3.6 Table of other secondary endpoints

Further secondary endpoints related to the efficacy of aflibercept 8 mg are summarised in the below table. The conclusions of the 36-week analysis were all confirmed at week 64.

Table 16. Other secondary endpoints

Secondary endpoints through week 64, full analysis set	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
Visual and anatomic outcomes			
Participants who gained at least 15 letters*	154/255 (60.4%)	156/253 (61.7%)	161/240 (67.1%)
Participants who achieved a letter score of at least 69*	179/255 (70.2%)	178/253 (70.4%)	181/240 (75.4%)
Participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF)*	167/253 (66.0%)	193/253 (76.3%)	171/240 (71.3%)
Change from baseline in NEI-VFQ-25 total score			
Baseline mean	78.98	79.39	78.15
LS mean change from baseline	7.21 (0.60)	6.10 (0.66)	6.67 (0.63)
Arithmetic mean *SD) change from baseline	6.91 (12.47)	5.92 (12.47)	7.01 (12.42)
Nr of participants with week 64 data: included/excluded due to ICE	255/15	253/15	240/15
Contrast	-	AFL 8mg Q8W/3 – AFL 2mg Q4W	AFL 8mg Q8W/5 – AFL 2mg Q4W
DF	-	529	524
t -value	-	-1.24	-0.62
p -value	-	0.2167	0.5340
Estimate for Contrast and two-sided 95% CI	-	-1.11 (-2.9,0.65)	-0.54 (-2.3,1.17)

* OC excluding values after ICE (full analysis set).

BL = Baseline; CI = Confidence Interval; DF = Degrees of Freedom; ICE = Intercurrent Event; LS = Least Squares; SD = Standard Deviation; SE = Standard Error An analysis of covariance (ANCOVA) was used with baseline NEI-VFQ-25 total score measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs. >=60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors. Intercurrent events were handled according to sensitivity estimand strategy as described in Table 4-2 in section 4.2.2.1 of the SAP. LOCF (last observation carried forward): last available observed value prior to ICE was used to impute missing data. (a) Based on a mix of observed and imputed assessments. (b) Based on observed assessments. (c) p-value for the two-sided test. (d) Estimate based on the ANCOVA model, was computed for the differences of 8q8/3 minus 2q4 and 8q8/5 minus 2q4, respectively with two-sided 95% CIs.

ICE = Intercurrent Event OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in the SAP. Missing cases will not be included in the denominator when calculating proportions.

5.2.3.7 Proportion of subjects who lost less than 15 letters in BCVA from baseline by visit at week 64

Table 17. Proportion of subjects who lost less than 15 letters in BCVA from baseline to week 64

Full analysis set - week 64	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298
Subjects who lost < 15 letters Num/Den (%)	291/301 (96.7%)	287/293 (98.0%)	288/298 (96.6%)

(a) CI=Miettinen-Nurminen confidence interval. (b) CI=Wald confidence interval.
Intercurrent events will be handled according to sensitivity estimand strategy for continuous endpoints as described in Table 4-2 in Section
4.2.2.1 of the SAP.
LOCF (last observation carried forward): last available observed value prior to ICE will be used to impute missing data.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals. 8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

5.2.4 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

5.2.5 Safety profile from QUASAR: Results at 36 weeks

5.2.5.1 Proportion of participants with any treatment-emergent adverse events through week 36

The proportions of patients who experienced any TEAEs were similar across all 3 treatment groups, with 66.9% in the aflibercept 8 mg Q8W/3 group and 63.8% in the aflibercept 8 mg Q8W/5 group (65.3% in the pooled 8 mg treatment groups) versus 66.8% in the aflibercept 2 mg Q4W group (Table 18).

5.2.5.2 Ocular treatment-emergent adverse events

The proportions of patients with any ocular TEAEs through week 36 were similar for aflibercept 8 mg Q8W/5 and aflibercept 2 mg Q4W groups, (32.6% versus 32.6%, respectively) and numerically higher in the aflibercept 8 mg Q8W/3 group compared to the aflibercept 2 mg Q4W group (39.9% versus 32.6%, respectively) (Table 18).

The proportions of patients with any ocular TEAEs in the study eye were numerically higher in the aflibercept 8 mg Q8W/3 group compared to the aflibercept 2 mg Q4W group (35.2% versus 28.2%, respectively). The percentage within aflibercept 8 mg Q8W/5 and aflibercept 2 mg Q4W groups, were similar (28.9% versus 28.2%, respectively) (Table 18). Most of the reported ocular TEAEs in the study eye were mild. In the pooled aflibercept 8 mg treatment groups, the proportions of patients with any ocular TEAE in the study eye of mild, moderate, and severe intensity were 24%, 7.1%, and 0.8%, respectively. In the aflibercept 2 mg group, the proportions were 19.3%, 7.0%, and 2.0%, respectively (Table 18).

5.2.5.3 Proportion of participants with any intervention-related treatment-emergent adverse events through week 36

The proportions of patients who experienced any intervention-related TEAEs were generally low. The percentage of patients with any intervention-related TEAEs was numerically higher in the aflibercept 8 mg Q8W/3 group compared to the aflibercept 2 mg Q4W group (4.8% versus 2.3%, respectively). The percentage within aflibercept 8 mg Q8W/5 and aflibercept 2 mg Q4W groups, were similar (2.3% versus 2.3%, respectively) (Table 18).

5.2.5.4 Ocular intervention-related treatment-emergent adverse events

Any intervention-related ocular TEAEs were reported in 4.1% of participants in the aflibercept Q8W/3 group and 2.0% of participants in the aflibercept Q8W/5 group (3% in the pooled 8 mg treatment groups) compared with 2.0% of participants in the aflibercept 2 mg group (Table 18).

Ocular TEAEs in the study eye judged to be related to the study drug were generally of low percentages. Ocular intervention-related TEAEs in the study eye were reported in 3% of participants in the pooled aflibercept 8 mg groups and 2% of participants in the aflibercept 2 mg group (Table 18). There were no ocular TEAEs in the study eye related to the study drug that were reported with a frequency of >1% in any treatment group (Table 18))

5.2.5.5 Proportion of participants with any treatment-emergent adverse events leading to discontinuation of the study drug through week 36

The proportions of patients who experienced any TEAEs leading to discontinuation of a study drug were similar across all groups and were generally low, with 0.7% in the aflibercept Q8W/3 group, 1.3% in the aflibercept Q8W/5 group (1% in the pooled 8 mg treatment groups) versus 1.3% in the aflibercept 2 mg group (Table 18).

5.2.5.6 Ocular treatment-emergent adverse events leading to discontinuation of the study drug

The proportions of patients who experienced any ocular TEAEs leading to discontinuation of the study drug were 0.2% in the pooled 8 mg treatment groups (0.3% in the Q8W/5 group and no incidence in the Q8W/3 group) versus 0.3% in the aflibercept 2 mg group (Table 18).

Ocular TEAEs in the study eye that led to discontinuation of the study drug affected few participants: 0.3% of patients in the aflibercept Q4W group, no such incidents in the aflibercept Q8W/3 group, and 0.3% in the aflibercept Q8W/5 group (0.2% for the pooled 8 mg treatment groups) (Table 18).

5.2.5.7 Non-ocular treatment-emergent adverse events leading to discontinuation of the study drug

Similarly, non-ocular TEAEs resulted in the discontinuation of the study drug in 0.8% of participants in the pooled aflibercept 8 mg treatment groups and 1% of participants in the aflibercept 2 mg group (Table 18).

5.2.5.8 Proportion of participants with treatment-emergent adverse events related to intravitreal injection procedure in the study eye through week 36

The proportions of ocular TEAEs related to the intravitreal injection procedure in the study eye were slightly higher in the aflibercept 8 mg groups compared to the aflibercept 2 mg group. Intravitreal injection procedure-related TEAEs in the study eye were reported in 10.7% of the participants in the pooled aflibercept 8 mg groups (13% in the Q8W/3 group and 8.4% in the Q8W/5 group) and 6.3% of participants in the aflibercept 2 mg group (Table 31). The most common ocular TEAE related to the intravitreal injection procedure in the study eye, reported in ≥3 participants, was conjunctival haemorrhage (1.7% in the Q4W group, 2.7% in the Q8W/3 and 2% in the Q8W/5 group) (Table 18).

5.2.5.9 Proportion of participants with any serious adverse events through week 36

The proportions of patients who experienced any treatment-emergent serious adverse events (TESAEs) were numerically higher in the aflibercept 2 mg group. Any TESAEs were reported in 8.2% of participants in the aflibercept Q8W/3 group, 8.7% in the aflibercept Q8W/5 group (8.5% in the pooled 8 mg treatment groups) and 10.6% of participants in the aflibercept 2 mg group (Table 18).

5.2.5.10 Ocular serious adverse events

The proportion of participants with ocular TESAEs was low in all treatment groups and numerically higher in the aflibercept 2 mg group. These TESAEs were reported in 1.4% of participants from the aflibercept Q8W/3 group and in 1.3% of participants from the aflibercept Q8W/5 group (1.4% in the pooled 8 mg treatment groups) versus 2.3% of participants from the aflibercept 2 mg group (Table 18).

5.2.5.11 Non-ocular serious adverse events

Non-ocular TESAEs were reported in 7.2% of participants in the aflibercept Q8W/3 group and 7.4% in the aflibercept Q8W/5 group (7.3% in the pooled 8 mg treatment groups) versus 8.3% in the aflibercept 2 mg group (Table 18).

Table 18. Overall summary of all adverse events through week 36

Safety analysis set [n (%)]	Aflibercept 2 mg	Aflibercept 8 mg		
	Q4W n=301	Q8W/3 n=293	Q8W/5 n=298	Pooled n=591
Any AE	206 (68.4%)	200 (68.3%)	203 (68.1%)	403 (68.2%)
Any pre-treatment AE	25 (8.3%)	28 (9.6%)	30 (10.1%)	58 (9.8%)
Any TEAE	201 (66.8%)	196 (66.9%)	190 (63.8%)	386 (65.3%)
Any post-treatment AE	1 (0.3%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Any ocular TEAE	98 (32.6%)	117 (39.9%)	97 (32.6%)	214 (36.2%)
Any ocular TEAE in the study eye	85 (28.2%)	103 (35.2%)	86 (28.9%)	189 (32.0%)
Eye disorders*				
Cataract	9 (3.0%)	5 (1.7%)	10 (3.4%)	15 (2.5%)
Conjunctival haemorrhage	6 (2.0%)	10 (3.4%)	7 (2.3%)	17 (2.9%)
Conjunctivitis allergic	4 (1.3%)	3 (1.0%)	2 (0.7%)	5 (0.8%)
Dry eye	6 (2.0%)	4 (1.4%)	5 (1.7%)	9 (1.5%)
Epiretinal membrane	6 (2.0%)	3 (1.0%)	7 (2.3%)	10 (1.7%)
Eye pain	3 (1.0%)	5 (1.7%)	4 (1.3%)	9 (1.5%)
Glaucoma	0	4 (1.4%)	1 (0.3%)	5 (0.8%)
Macular thickening	0	5 (1.7%)	0	5 (0.8%)
Ocular hypertension	4 (1.3%)	4 (1.4%)	2 (0.7%)	6 (1.0%)

Punctate keratitis	5 (1.7%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
RVO	1 (0.3%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Visual acuity reduced	4 (1.3%)	12 (4.1%)	8 (2.7%)	20 (3.4%)
Vitreous detachment	2 (0.7%)	8 (2.7%)	9 (3.0%)	17 (2.9%)
Vitreous floaters	3 (1.0%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Vitreous haemorrhage	0	3 (1.0%)	2 (0.7%)	5 (0.8%)
Investigations*				
Intraocular pressure increased	5 (1.7%)	16 (5.5%)	15 (5.0%)	31 (5.2%)
Infections and infestations*				
Conjunctivitis	2 (0.7%)	3 (1.0%)	2 (0.7%)	5 (0.8%)
Injury, poisoning and procedural complications*				
Intra-ocular injection complication	1 (0.3%)	5 (1.7%)	0	5 (0.8%)
Any ocular TEAE in the fellow eye	47 (15.6%)	49 (16.7%)	41 (13.8%)	90 (15.2%)
Any non-ocular TEAE	151 (50.2%)	138 (47.1%)	152 (51.0%)	290 (49.1%)
Any intervention-related TEAE	7 (2.3%)	14 (4.8%)	7 (2.3%)	21 (3.6%)
Any ocular intervention-related TEAE	6 (2.0%)	12 (4.1%)	6 (2.0%)	18 (3.0%)
Any ocular intervention-related TEAE in the study eye	6 (2.0%)	12 (4.1%)	6 (2.0%)	18 (3.0%)
Eye disorders				
Anterior chamber disorder	0	1 (0.3%)	0	1 (0.2%)
Blindness	0	0	1 (0.3%)	1 (0.2%)
Conjunctival haemorrhage	0	0	1 (0.3%)	1 (0.2%)
Epiretinal membrane	1 (0.3%)	0	0	0

Eye inflammation	1 (0.3%)	0	0	0
Macular degeneration	2 (0.7%)	0	0	0
Macular oedema	0	1 (0.3%)	0	1 (0.2%)
Macular thickening	0	1 (0.3%)	0	1 (0.2%)
Retinal vasculitis	0	0	1 (0.3%)	1 (0.2%)
Visual acuity reduced	2 (0.7%)	2 (0.7%)	0	2 (0.3%)
Vitreous detachment	0	1 (0.3%)	0	1 (0.2%)
Any ocular intervention-related TEAE in the fellow eye	0	0	0	0
Any non-ocular intervention-related TEAE	1 (0.3%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Any TEAE related to the injection procedure	20 (6.6%)	38 (13.0%)	25 (8.4%)	63 (10.7%)
Any ocular TEAE related to the injection procedure	19 (6.3%)	38 (13.0%)	25 (8.4%)	63 (10.7%)
Any ocular TEAE related to the injection procedure in the study eye	19 (6.3%)	38 (13.0%)	25 (8.4%)	63 (10.7%)
Eye disorders*				
Conjunctival haemorrhage	5 (1.7%)	8 (2.7%)	6 (2.0%)	14 (2.4%)
Any ocular TEAE related to the injection procedure in the fellow eye	0	1 (0.3%)	0	1 (0.2%)
Any non-ocular TEAE related to the injection procedure	1 (0.3%)	0	0	0
Any TEAE related to protocol-required procedure	6 (2.0%)	9 (3.1%)	11 (3.7%)	20 (3.4%)
Any ocular TEAE related to protocol-required procedure	3 (1.0%)	5 (1.7%)	6 (2.0%)	11 (1.9%)
Any ocular TEAE related to protocol-required procedures in the study eye	3 (1.0%)	5 (1.7%)	6 (2.0%)	11 (1.9%)

Any ocular TEAE related to protocol-required procedures in the fellow eye	0	0	0	0
Any non-ocular TEAE related to protocol-required procedure	3 (1.0%)	4 (1.4%)	5 (1.7%)	9 (1.5%)
Any TEAE related to commercial aflibercept 2mg (of fellow eye)	0	0	0	0
Any TEAE leading to discontinuation of the study drug	4 (1.3%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Any ocular TEAE leading to discontinuation of the study drug	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Any ocular TEAE leading to discontinuation of the study drug in the study eye	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Any ocular TEAE leading to discontinuation of the study drug in the fellow eye	0	0	0	0
Any non-ocular TEAE leading to discontinuation of the study drug	3 (1.0%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Any TEAE of special interest	9 (3.0%)	1 (0.3%)	5 (1.7%)	6 (1.0%)
Any TEAE of APTC events	5 (1.7%)	0	3 (1.0%)	3 (0.5%)
Any TEAE of hypertension	14 (4.7%)	24 (8.2%)	24 (8.1%)	48 (8.1%)
Any TEAE of intraocular inflammation in the study eye	4 (1.3%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Any TEAE of nasal mucosal finding	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Maximum intensity for any ocular TEAE				
Mild intensity for any ocular TEAE in the study eye	58 (19.3%)	76 (25.9%)	66 (22.1%)	142 (24.0%)
Moderate intensity for any ocular TEAE in the study eye	21 (7.0%)	25 (8.5%)	17 (5.7%)	42 (7.1%)
Severe intensity for any ocular TEAE in the study eye	6 (2.0%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Severe intensity for any ocular TEAE in the fellow eye	0	1 (0.3%)	0	1 (0.2%)
Maximum intensity for any non-ocular TEAE				
Mild intensity for any non-ocular TEAE	84 (27.9%)	86 (29.4%)	95 (31.9%)	181 (30.6%)

Moderate intensity for any non-ocular TEAE	51 (16.9%)	38 (13.0%)	45 (15.1%)	83 (14.0%)
Severe intensity for any non-ocular TEAE	16 (5.3%)	14 (4.8%)	12 (4.0%)	26 (4.4%)
Any serious AE (SAE)	34 (11.3%)	25 (8.5%)	32 (10.7%)	57 (9.6%)
Any pre-treatment SAE	2 (0.7%)	0	5 (1.7%)	5 (0.8%)
Any serious TEAE (TESAE)	32 (10.6%)	24 (8.2%)	26 (8.7%)	50 (8.5%)
Any post-treatment SAE	1 (0.3%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Any ocular TESAE	7 (2.3%)	4 (1.4%)	4 (1.3%)	8 (1.4%)
Any ocular TESAE in the study eye	7 (2.3%)	3 (1.0%)	4 (1.3%)	7 (1.2%)
Any ocular TESAE in the fellow eye	0	1 (0.3%)	0	1 (0.2%)
Any non-ocular TESAE	25 (8.3%)	21 (7.2%)	22 (7.4%)	43 (7.3%)
Any intervention-related TESAE	2 (0.7%)	0	1 (0.3%)	1 (0.2%)
Any ocular intervention-related TESAE	2 (0.7%)	0	1 (0.3%)	1 (0.2%)
Any ocular intervention-related TESAE in the study eye	2 (0.7%)	0	1 (0.3%)	1 (0.2%)
Any ocular intervention-related TESAE in the fellow eye	0	0	0	0
Any non-ocular intervention-related TESAE	0	0	0	0
Any TESAE related to the injection procedure	4 (1.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Any ocular TESAE related to the injection procedure	4 (1.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Any ocular TESAE related to the injection procedure in the study eye	4 (1.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Any ocular TESAE related to the injection procedure in the fellow eye	0	0	0	0
Any non-ocular TESAE related to the injection procedure	0	0	0	0

Any TESAE related to protocol-required procedure	0	0	0	0
Any ocular TESAE related to protocol-required procedure	0	0	0	0
Any ocular TESAE related to protocol-required procedure in the study eye	0	0	0	0
Any ocular TESAE related to protocol-required procedure in the fellow eye	0	0	0	0
Any non-ocular TESAE related to protocol-required procedure	0	0	0	0
Any TESAE of special interest	6 (2.0%)	1 (0.3%)	4 (1.3%)	5 (0.8%)
Any TESAE of APTC events	4 (1.3%)	0	3 (1.0%)	3 (0.5%)
Any TESAE of hypertension	1 (0.3%)	0	0	0
Any TESAE of intraocular inflammation of the study eye	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Any TESAE of nasal mucosal finding	1 (0.3%)	0	0	0
Maximum intensity for any ocular TESAE				
Mild intensity for any ocular TESAE in the study eye	0	0	1 (0.3%)	1 (0.2%)
Moderate intensity for any ocular TESAE in the study eye	4 (1.3%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Severe intensity for any ocular TESAE in the study eye	3 (1.0%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Severe intensity for any ocular TESAE in the fellow eye	0	1 (0.3%)	0	1 (0.2%)
Maximum intensity for any non-ocular TESAE				
Mild intensity for any non-ocular TESAE	1 (0.3%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Moderate intensity for any non-ocular TESAE	10 (3.3%)	8 (2.7%)	9 (3.0%)	17 (2.9%)
Severe intensity for any non-ocular TESAE	14 (4.7%)	11 (3.8%)	10 (3.4%)	21 (3.6%)

Total number of deaths	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Any AE with outcome death	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Any pre-treatment AE with outcome death	0	0	0	0
Any TEAE with outcome death	2 (0.7%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Any post-treatment AE with outcome death	0	0	1 (0.3%)	1 (0.2%)
Deaths not attributed to an AE	0	0	0	0

Pre-treatment adverse events are defined as AEs that start before the first administration of the study intervention.

TEAEs are defined as AEs that started in the time frame from the first injection to the last injection (active or sham) in the study plus 30 days.

For the participants who have not discontinued study treatment prematurely (i.e., are 'ongoing') at the week 36 analysis, all AEs that started at first injection or later will be considered treatment-emergent.

Post-treatment adverse events are defined as AEs that start more than 30 days after the stop of the study intervention.

Only the most severe intensity is counted for multiple occurrences of the same AE in one individual. 'Missing' is considered to be the lowest category of intensity.

Adverse Events of Special Interest are arterial thromboembolic events, including cerebrovascular ischemic events and cardiovascular ischemic events.

* Includes only those subjects with at least 3 preferred terms ≥1% in any group (Q4W, Q8W/3 or Q8W/5).

AE: Adverse event; APTC: Anti-platelet trialists' collaboration; Q4W: Every 4 weeks, Q8W/3: Every 8 weeks; after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals; RVO: Retinal vein occlusion; SAE: Serious adverse event; TEAE: Treatment-emergent adverse event; TESAE: Treatment-emergent serious adverse event

5.2.5.12 First ocular treatment-emergent serious adverse events of study eye at week 36

Table 19. First ocular treatment-emergent serious adverse events of study eye: number of subjects by primary system organ class and preferred term

Preferred term - Week 36	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298	Pooled 8 mg N=591
Number (%) of subjects with at least one such adverse event	7 (2.3%)	3 (1.0%)	4 (1.3%)	7 (1.2%)
Eye disorders	5 (1.7%)	0	4 (1.3%)	4 (0.7%)
Cataract	0	0	1 (0.3%)	1 (0.2%)
Macular hole	2 (0.7%)	0	0	0
Retinal artery occlusion	1 (0.3%)	0	0	0
Retinal detachment	1 (0.3%)	0	0	0
Retinal vasculitis	0	0	1 (0.3%)	1 (0.2%)
Retinal vein occlusion	0	0	1 (0.3%)	1 (0.2%)
Visual acuity reduced	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
General disorders and administration site conditions	0	1 (0.3%)	0	1 (0.2%)
Oedema	0	1 (0.3%)	0	1 (0.2%)
Infections and infestations	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Endophthalmitis	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	0	1 (0.3%)	0	1 (0.2%)
Skin laceration	0	1 (0.3%)	0	1 (0.2%)

For the frequencies of the preferred terms only the first event is considered. If multiple events occurred on the same day only the event which is first in alphabetical order is considered.
MedDRA Medical Dictionary for Regulatory Activities. TEAE Treatment-emergent adverse event.
TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals. 8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.
All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals.

5.2.5.13 Most severe ocular treatment-emergent serious adverse events of study eye at week 36

Table 20. Most severe ocular treatment-emergent serious adverse events of study eye: number of subjects by primary system organ class and preferred term (safety analysis)

Preferred term - week 36	Aflibercept 2mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298	Pooled 8 mg N=591
Number (%) of subjects with at least one such adverse event	7 (2.3%)	3 (1.0%)	4 (1.3%)	7 (1.2%)
Eye disorders	5 (1.7%)	0 (0%)	4 (1.3%)	4 (0.7%)
Cataract	0 (0%)	0 (0%)	1 (0.3%)	1 (0.2%)
Macular hole	2 (0.7%)	0 (0%)	0(0%)	0 (0%)
Retinal artery occlusion	1 (0.3%)	0 (0%)	0(0%)	0 (0%)
Retinal detachment	1 (0.3%)	0 (0%)	0(0%)	0 (0%)
Retinal vasculitis	0 (0%)	0 (0%)	1 (0.3%)	1 (0.2%)
Retinal vein occlusion	0 (0%)	0 (0%)	1 (0.3%)	1 (0.2%)
Visual acuity reduced	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.2%)
General disorders and administration site conditions	0 (0%)	1 (0.3%)	0(0%)	1 (0.2%)
Oedema	0 (0%)	1 (0.3%)	0(0%)	1 (0.2%)
Infections and infestations	2 (0.7%)	1 (0.3%)	0(0%)	1 (0.2%)
Endophthalmitis	2 (0.7%)	1 (0.3%)	0(0%)	1 (0.2%)
Injury, poisoning and procedural complications	0 (0%)	1 (0.3%)	0(0%)	1 (0.2%)
Skin laceration	0 (0%)	1 (0.3%)	0(0%)	1 (0.2%)

For the frequencies of the preferred terms only the most severe event is considered. If multiple events occurred with the same severity only the event which is first in alphabetical order is considered.
MedDRA Medical Dictionary for Regulatory Activities. TEAE Treatment-emergent adverse event.
TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals. 8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.
All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals.

5.2.6 Safety profile from QUASAR: Results at 64 weeks

5.2.6.1 Overview of safety at 64 weeks

The below overview of the safety results at week 64 of the QUASAR study suggest that the safety profiles of aflibercept 2 mg and aflibercept 8 mg are comparable. The

incidence of TEAEs and SAEs reported during the study was similar across the treatment groups (Table 21).

The results of the subgroup analyses by RVO types for ocular TEAEs in the study eye and non-ocular TEAEs were generally similar to those seen in the entire safety population and did not suggest clinically relevant differences among the treatment groups.

The analysis of specific safety topics (hypertension, intraocular inflammation, and nasal mucosal findings) did not show any clinically meaningful differences among the treatment groups. (Table 21)

Table 21. Topline safety results through week 64

Safety analysis set (%)	Aflibercept 2 mg	Aflibercept 8mg		
	Q4W N=301	**Q8W/3** N=293	**Q8W/5** N=298	**Pooled** N=591
Any AE	81.1%	80.2%	78.2%	79.2%
Any TEAE	78.4%	78.5%	75.5%	77.0%
Any ocular TEAE	47.2%	50.5%	44.3%	47.4%
Any non-ocular TEAE	62.8%	61.8%	62.8%	62.3%
Any TEAE leading to d/c of intervention	1.7%	1.0%	2.0%	1.5%
Any SAE	16.3%	13.3%	15.1%	14.2%
Any TESAE	14.6%	12.6%	12.8%	12.7%
Any ocular TESAE	2.7%	1.7%	1.7%	1.7%
Any non-ocular TESAE	12.0%	11.3%	33 (11.1%	11.2%

Pre-treatment adverse events are defined as AEs that start before first administration of study intervention.

TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.

Post-treatment adverse events are defined as AEs that start more than 30 days after the stop of study intervention.

Only the most severe intensity is counted for multiple occurrences of the same AE in one individual. 'Missing' is considered to be the lowest category of intensity.

Adverse Event of Special Interest (AESI) are arterial thromboembolic events including cerebrovascular ischemic events and cardiovascular ischemic events.

AE: Adverse event; APTC: Anti-platelet trialists' collaboration; Q4W: Every 4 weeks, Q8W/3: Every 8 weeks; after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals; TEAE: Treatment-emergent adverse event

Table 22. Selected TEAEs of special interest through week 64

Safety analysis set (%)	Aflibercept 2 mg	Aflibercept 8mg		
	Q4W	**Q8W/3**	**Q8W/5**	**Pooled**
	N=301	N=293	N=298	N=591
Any TEAE of hypertension	7.0%	13.0%	9.7%	11.3%
Any TEAE of intraocular inflammation of study eye	1.7%	1.4%	0.7%	1.0%
Any TEAE of nasal mucosal finding	0.7%	1.0%	0.3%	0.7%
APTC events	2.0%	0.7%	2.3%	1.5%

Pre-treatment adverse events are defined as AEs that start before first administration of study intervention.

TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.

Post-treatment adverse events are defined as AEs that start more than 30 days after the stop of study intervention.

Only the most severe intensity is counted for multiple occurrences of the same AE in one individual. 'Missing' is considered to be the lowest category of intensity.

Adverse Event of Special Interest (AESI) are arterial thromboembolic events including cerebrovascular ischemic events and cardiovascular ischemic events.

AE: Adverse event; APTC: Anti-platelet trialists' collaboration; Q4W: Every 4 weeks, Q8W/3: Every 8 weeks; after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals; TEAE: Treatment-emergent adverse event

5.2.6.2 Proportion of participants with ocular TEAEs through week 64

Table 23. Proportion of participants with ocular TEAEs through week 64, (> 2% in any arm)

Safety analysis set [n (%)]	Aflibercept 2 mg	Aflibercept 8mg		
	Q4W N=301	Q8W/3 N=293	Q8W/5 N=298	Pooled N=591
Number of Patients ≥ 1 AE, n (%)	127 (42.2%)	134 (45.7%)	118 (39.6%)	252 (42.6%)
Cataract	17 (5.6%)	11 (3.8%)	18 (6.0%)	29 (4.9%)
Conjunctival haemorrhage	8 (2.7%)	14 (4.8%)	12 (4.0%)	26 (4.4%)
Dry eye	9 (3.0%)	4 (1.4%)	9 (3.0%)	13 (2.2%)
Epiretinal membrane	6 (2.0%)	6 (2.0%)	10 (3.4%)	16 (2.7%)
Macular oedema	6 (2.0%)	10 (3.4%)	5 (1.7%)	15 (2.5%)
Macular thickening	8 (2.7%)	12 (4.1%)	1 (0.3%)	13 (2.2%)
Punctate keratitis	7 (2.3%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Visual acuity reduced	12 (4.0%)	16 (5.5%)	9 (3.0%)	25 (4.2%)
Vitreous detachment	4 (1.3%)	9 (3.1%)	10 (3.4%)	19 (3.2%)
Intraocular pressure increased	8 (2.7%)	19 (6.5%)	16 (5.4%)	35 (5.9%)

Adverse events are sorted by alphabetical order of the MedDRA classification. A participant is counted only once within each primary SOC and preferred term.

TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.

AE: Adverse event; Q4W: Every 4 weeks, Q8W/3: Every 8 weeks; after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals; TEAE: Treatment-emergent adverse event

5.2.6.3 Proportion of participants with non-ocular TEAEs through week 64

Table 24. Proportion of participants with non-ocular TEAEs through week 64, (> 2% in any arm)

Safety analysis set [n (%)]	Aflibercept 2 mg	Aflibercept 8mg		
	Q4W N=301	Q8W/3 N=293	Q8W/5 N=298	Pooled N=591
Number of Patients ≥ 1 AE, n (%)	189 (62.8%)	181 (61.8%)	187 (62.8%)	368 (62.3%)
COVID-19	9 (3.0%)	17 (5.8%)	12 (4.0%)	29 (4.9%)
Herpes zoster	7 (2.3%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Influenza	13 (4.3%)	11 (3.8%)	6 (2.0%)	17 (2.9%)
Nasopharyngitis	20 (6.6%)	25 (8.5%)	27 (9.1%)	52 (8.8%)
Upper respiratory tract infection	8 (2.7%)	8 (2.7%)	3 (1.0%)	11 (1.9%)
Urinary tract infection	13 (4.3%)	8 (2.7%)	15 (5.0%)	23 (3.9%)
Hypercholesterolaemia	5 (1.7%)	5 (1.7%)	8 (2.7%)	13 (2.2%)
Hyperlipidaemia	9 (3.0%)	3 (1.0%)	3 (1.0%)	6 (1.0%)
Arthralgia	7 (2.3%)	6 (2.0%)	6 (2.0%)	12 (2.0%)
Back pain	7 (2.3%)	3 (1.0%)	5 (1.7%)	8 (1.4%)
Headache	8 (2.7%)	10 3.4%)	7 (2.3%)	17 (2.9%)
Cough	7 (2.3%)	6 (2.0%)	3 (1.0%)	9 (1.5%)
Hypertension	15 (5.0%)	31 (10.6%)	25 (8.4%)	56 (9.5%)

Adverse events are sorted by alphabetical order of the MedDRA classification. A participant is counted only once within each primary SOC and preferred term.

TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.

AE: Adverse event; Q4W: Every 4 weeks, Q8W/3: Every 8 weeks; after 3 initial injections at 4-week intervals; Q8W/5: Every 8 weeks, after 5 initial injections at 4-week intervals; All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals; TEAE: Treatment-emergent adverse event

5.2.6.4 First ocular treatment-emergent serious adverse events of study eye at week 64

Table 25. First ocular treatment-emergent serious adverse events of study eye: number of subjects by primary system organ class and preferred term (safety analysis set)

Preferred term - Week 64	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298	Pooled 8 mg N=591
Number (%) of subjects with at least one such adverse event	8 (2.7%)	5 (1.7%)	5 (1.7%	10 (1.7%)
Eye disorders	5 (1.7%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Cataract	0	0	1 (0.3%)	1 (0.2%)
Glaucoma	0	1 (0.3%)	0	1 (0.2%)
Macular hole	2 (0.7%)	0	0	0
Retinal artery occlusion	1 (0.3%)	0	0	0
Retinal detachment	1 (0.3%)	0	0	0
Retinal vasculitis	0	0	1 (0.3%)	1 (0.2%)
Retinal vein occlusion	0	0	1 (0.3%)	1 (0.2%)
Visual acuity reduced	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Vitritis	0	1 (0.3%)	0	1 (0.2%)
General disorders and administration site conditions	0	1 (0.3%)	0	1 (0.2%)
Oedema	0	1 (0.3%)	0	1 (0.2%)
Infections and infestations	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Endophthalmitis	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Posterior capsule rupture	0	0	1 (0.3%)	1 (0.2%)
Skin laceration	0	1 (0.3%)	0	1 (0.2%)

For the frequencies of the preferred terms only the first event is considered. If multiple events occurred on the same day only the event which is first in alphabetical order is considered.
MedDRA Medical Dictionary for Regulatory Activities. TEAE Treatment-emergent adverse event.
TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals. 8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.
All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals.

5.2.6.5 Most severe ocular treatment-emergent serious adverse events of study eye at week 64

Table 26. Most severe ocular treatment-emergent serious adverse events of study eye: number of subjects by primary system organ class and preferred term (safety analysis)

Preferred term - week 64	Aflibercept 2 mg Q4W n=301	Aflibercept 8 mg Q8W/3 n=293	Aflibercept 8 mg Q8W/5 n=298	Pooled 8 mg N=591
Number (%) of subjects with at least one such adverse event	8 (2.7%)	5 (1.7%)	5 (1.7%)	10 (1.7%)
Eye disorders	5 (1.7%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Cataract	0 (0%)	0 (0%)	1 (0.3%)	1 (0.2%)
Glaucoma	0 (0%)	1 (0.3%)	0 (0%)	1 (0.2%)
Macular hole	2 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Retinal artery occlusion	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Retinal detachment	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)
Retinal vasculitis	0 (0%)	0 (0%)	1 (0.3%)	1 (0.2%)
Retinal vein occlusion	0 (0%)	0 (0%)	1 (0.3%)	1 (0.2%)
Visual acuity reduced	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.2%)
Vitritis	0 (0%)	1 (0.3%)	0 (0%)	1 (0.2%)
General disorders and administration site conditions	0 (0%)	1 (0.3%)	0 (0%)	1 (0.2%)
Oedema	0 (0%)	1 (0.3%)	0 (0%)	1 (0.2%)
Infections and infestations	3 (1.0%)	1 (0.3%)	0 (0%)	1 (0.2%)
Endophthalmitis	3 (1.0%)	1 (0.3%)	0 (0%)	1 (0.2%)
Injury, poisoning and procedural complications	0 (0%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Posterior capsule rupture	0 (0%)	0 (0%)	1 (0.3%)	1 (0.2%)
Skin laceration	0 (0%)	1 (0.3%)	0 (0%)	1 (0.2%)

For the frequencies of the preferred terms only the most severe event is considered. If multiple events occurred with the same severity only the event which is first in alphabetical order is considered.
MedDRA Medical Dictionary for Regulatory Activities. TEAE Treatment-emergent adverse event.
TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals. 8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.
All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals.

5.2.7 Method of synthesis

Not relevant for the application, as the intervention is directly compared to the current standard of care in the provided study.

5.2.8 Results from the comparative analysis

This section is not relevant for the application, as the intervention is directly compared to the current standard of care in the provided study.

Table 27. Results from the comparative analysis of [intervention] vs. [comparator] for [patient population]

Outcome measure	Intervention	Comparator	Result
[Outcome measure 1], time point	N/A	N/A	N/A
[Outcome measure 2], time point	N/A	N/A	N/A
[Outcome measure 3], time point	N/A	N/A	N/A
OS	N/A	N/A	N/A
Proportion of patients achieving ASAS40 (week 12)	N/A	N/A	N/A
Proportion of patients with AE ≥ grade 3	N/A	N/A	N/A

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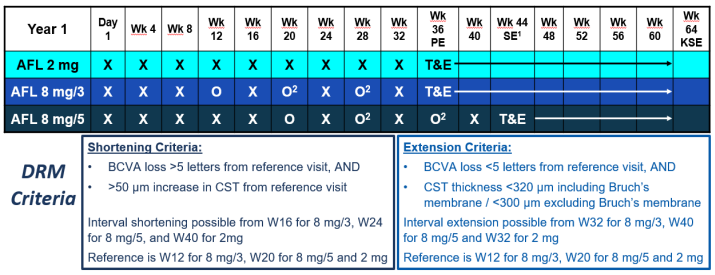
Appendix A. Main characteristics of studies included

Table 28. Main characteristics of studies included

Trial name: QUASAR	NCT number: NCT05850520
Objective	The primary objective of the study was to determine if treatment with aflibercept 8 mg at intervals of 8 weeks (after initial 3 or 5 monthly doses) provides non-inferior BCVA change compared with aflibercept 2 mg every 4 weeks, from the date of randomization through 36 weeks of treatment and to determine if treatment with aflibercept 8 mg Q8W requires fewer injections compared to aflibercept 2 mg Q4W. The study also evaluates the safety and tolerability of aflibercept 8 mg.
Publications – title, author, journal, year	Not published
Study type and design	QUASAR is an ongoing multicenter, randomized, double-masked, active-controlled, phase 3 study of the efficacy and safety of aflibercept 8 mg compared with aflibercept 2 mg in participants with treatment-naïve MO secondary to RVO. The study consisted of a test (screening) phase, a treatment phase and an end-of-study phase. The pre-planned primary analysis was conducted at 36 weeks. Each participant was in the study for up to 64 weeks (up to 60 weeks in the treatment phase followed by a monitoring period until week 64). In the trial, patients were randomized in a 1:1:1 ratio into three groups to receive either: • aflibercept 8 mg administered with 3 initial monthly doses followed by an extension of treatment interval to 8 weeks (Q8W/3) and further adjustment of intervals according to treatment response; • aflibercept 8 mg administered with 5 initial monthly doses followed by an extension of treatment interval to 8 weeks (Q8W/5) and further adjustment of intervals according to treatment response; or • aflibercept 2 mg every 4 weeks (Q4W) until Week 32, followed by adjustment of intervals according to treatment response. Patients in the aflibercept 8 mg groups can have their dosing intervals shortened to a minimum of every 4 weeks throughout the trial if protocol-defined criteria for disease progression are met. Dosing intervals may be extended based on protocol-defined criteria starting at week 32 for patients who receive aflibercept 2 mg or aflibercept 8 mg after 3 initial monthly doses or at week 40 for patients who receive

Trial name: QUASAR	NCT number: NCT05850520

aflibercept 8 mg after 5 initial monthly doses, with follow-up planned through week 64.



AFL: aflibercept, BCVA: best-corrected visual acuity, CST: central subfield thickness, DRM: dose regimen modification, KSE: key secondary endpoint, O: sham injection visit, PE: primary endpoint, SE: secondary endpoint, SD-OCT: spectral domain optical coherence tomography, T&E: treat and extend, Wk: week, X: active injection visit, -:no injection, 8 mg/3=8 mg Q8W after 3 initial Q4W doses, 8 mg/5: 8 mg Q8W after 5 initial Q4W doses.

[1]Secondary endpoint BCVA change from baseline to Week 44 for 2 mg and 8 mg/5 groups.

[2]Participants meeting interval shortening criteria at any dosing visit starting from Week 16 for 8 mg/3, Week 24 for 8 mg/5 or Week 40 for 2 mg have their dosing interval shortened by 4 weeks. Interval extension is possible from Week 32 for 8 mg/3, from Week 40 for 8 mg/5, and from Week 32 for 2 mg depending on DRM.

Randomization was stratified by RVO type (CRVO or HRVO vs. BRVO), geographic region (Japan vs. rest of APC vs. America vs. Europe), and baseline BCVA (<60 vs ≥60 letters) to ensure balanced distribution of the treatment groups within each stratum.

One visit by the patient to the study site was planned during the screening phase, followed by visits approximately every 4 weeks (16 in total) during treatment and one visit at the end of the study.

Sample size (n)	892 patients were enrolled in the study
Main inclusion criteria	• Adult ≥18 years of age (or country's legal age of adulthood if the legal age is >18 years) at the time of signing the informed consent. • Treatment-naïve macular edema involving the foveal center secondary to RVO (BRVO, HRVO, or CRVO) diagnosed within 16 weeks (112 days) before the screening visit in the study eye. • Early Treatment Diabetic Retinopathy Study BCVA letter score of 73 to 24 (20/40 to 20/320) at screening and baseline visits in the study eye. Decrease in BCVA determined to be primarily the result of RVO in the study eye.

Trial name: QUASAR		NCT number: NCT05850520
	• Mean CST ≥300 µm on optical coherence tomography (OCT) if excluding Bruch's membrane (e.g., Cirrus or Topcon) or ≥320 µm if including Bruch's membrane (e.g., Heidelberg Spectralis), confirmed by the reading center at the screening visit and by the site at baseline visit in the study eye. • Capable of giving signed informed consent form (ICF) by study participant or legally acceptable representative, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. • US participants will be required to have a Health Insurance Portability and Accountability Act (HIPAA) authorization; in other countries, as applicable according to national laws. • Women of childbearing potential (WOCBP) or men who are sexually active with partners of childbearing potential must agree to use highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 4 months after the last administration of study intervention. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for participation in clinical studies	
Main exclusion criteria	• Concurrent disease that causes substantial decrease of BCVA, is expected to limit BCVA recovery or is likely to require medical or surgical intervention during the study in the study eye. • Presence or history of the following ocular conditions: 1. Advanced age-related macular degeneration (neovascular AMD or geographic atrophy) in the study eye. 2. Diabetic macular edema or diabetic retinopathy, defined in diabetic participants as diabetic retinopathy lesions outside the area of the vein occlusion in the study eye and anywhere in the retina in the fellow eye. 3. Anterior segment neovascularization, vitreous hemorrhage, retinal detachment in the study eye. 4. Vitreomacular traction, epiretinal membrane or structural damage to the macula that is considered by the Investigator to significantly affect central vision or preclude improvement in vision in the study eye. 5. Macular hole of stage 2 and above in the study eye. 6. Myopia of a spherical equivalent of at least 8 diopters prior to any refractive or cataract surgery in the study eye.	

7. Corneal transplant or corneal dystrophy in the study eye.
8. Idiopathic or autoimmune uveitis in the study or in the fellow eye.

- Presence of the following ocular conditions at screening or baseline visit:
    1. Significant media opacities, including cataract, that interfere with BCVA, or imaging assessments (e.g., fundus photography [FP], OCT) in the study eye.
    2. Aphakia, or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium-aluminum-garnet [YAG] posterior capsulotomy performed more than 30 days before the screening visit), in the study eye.
    3. Uncontrolled glaucoma (defined as IOP >25 mmHg despite treatment with anti-glaucoma medication); or history or likely future need of glaucoma surgery in the study eye.
    4. Intraocular inflammation/infection (including trace, or above, cells in the anterior chamber and/or vitreous) within 12 weeks (84 days) of the screening visit in the study or in the fellow eye.
    5. Extraocular or periocular infection or inflammation (including infectious blepharitis, keratitis, scleritis, or conjunctivitis) in the study or in the fellow eye.
- Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg) at the screening visit or baseline visit.
- Uncontrolled diabetes mellitus, defined by hemoglobin A1c (HbA1c) >12% at the screening visit.
- History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) before the screening visit or between screening and baseline visits.
- Renal failure requiring dialysis, or renal transplant at screening or potentially during the study.
- Any prior or concomitant ocular or systemic treatment (with an investigational or approved, anti-VEGF or other agent) or surgery for RVO in the study eye.
- Previous administration of systemic anti-angiogenic medications for any condition.
- Prior treatment of the study eye with any of the following drugs (any route of ophthalmic administration) or procedures:
    1. Anti-angiogenic drugs at any time including investigational therapy (e.g., with anti-angiopoietin/anti-VEGF bispecific monoclonal antibodies).

Trial name: QUASAR		NCT number: NCT05850520
	2. Previous use topical steroids within 4 weeks (28 days) from the screening visit, or intraocular or periocular steroids within 16 weeks (112 days) from the screening visit, or steroid implants at any time. 3. Previous treatment with intraocular or periocular implant, gene therapy, or cell therapy at any time. 4. Treatment with ocriplasmin at any time. 5. Vitreoretinal surgery (including scleral buckling) at any time. 6. Any intraocular surgery, including cataract surgery, within 12 weeks (84 days) before the screening visit. 7. Previous treatment with retinal laser photocoagulation. • Prior treatment of the fellow eye with any of the following: a. Gene therapy, or cell therapy in the fellow eye at any time. • Participation in other clinical studies requiring administration of investigational treatments (other than vitamins and minerals) at the time of screening visit, or within 30 days or 5 half-lives of administration of the previous study intervention, whichever is longer.	
Intervention	• aflibercept 8 mg administered with 3 initial monthly doses followed by an extension of treatment interval to 8 weeks (Q8W/3) and further adjustment of intervals according to treatment response. • aflibercept 8 mg administered with 5 initial monthly doses followed by an extension of treatment interval to 8 weeks (Q8W/5) and further adjustment of intervals according to treatment response.	
Comparator(s)	• aflibercept 2 mg every 4 weeks (Q4W) until Week 32, followed by adjustment of intervals according to treatment response.	
Follow-up time	Week 36 and 64	
Primary, secondary and exploratory endpoints	The primary endpoint was the mean change from baseline in BCVA measured by the ETDRS letter score at week 36. For the primary analysis, non-inferiority of aflibercept 8 mg Q8W/3 and Q8W/5 to aflibercept 2 mg Q4W in the primary endpoint was tested, with a non-inferiority margin of 4 letters. The key secondary efficacy endpoint was a number of active injections from baseline to week 64. **Primary endpoint** ▪ Change from baseline in BCVA measured by the ETDRS letter score at Week 36	

Trial name: QUASAR	NCT number: NCT05850520

Key secondary endpoint

- Number of active injections from baseline to Week 64

Secondary – Efficacy

- Number of active injections from baseline to Week 36
- Change from baseline in BCVA measured by the ETDRS letter score at Week 44[2]
- Change from baseline in BCVA measured by the ETDRS letter score at Week 64
- Participant gaining at least 15 letters in BCVA from baseline at Weeks 36 and 64
- Participant achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Weeks 36 and 64
- Participant having no IRF and no SRF in the center subfield at Weeks 36 and 64
- Change from baseline in CST at Weeks 36 and 64
- Change from baseline in NEI-VFQ-25 total score at Weeks 36 and 64

Secondary – Safety

- Occurrence of TEAEs and SAEs through Weeks 36 and 64

Secondary – Other

- Participant dosed only Q8W through Week 36 in the 8 mg Q8W group
- Participant having last treatment interval ≥12 or of 16 weeks at Week 64
- Participant having next intended interval ≥12, ≥16 or of 20 weeks at Week 64
- Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Weeks 36 and 64

Exploratory

- Change from baseline in BCVA measured by the ETDRS letter score at each visit
- Participant with vision changes of at least 5, 10, or 15 letters in BCVA from baseline at each visit
- Participant with no IRF and no SRF in the center subfield at each visit
- Time to fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield)
- Participant having sustained fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield)
- Change in area of retinal ischemia at Weeks 36 and 64
- Change in the area of fluorescein leakage at Weeks 36 and 64
- Evaluation of clinical efficacy parameters by repertoire or frequency of genetic alterations (genomics substudy)

Trial name: QUASAR	NCT number: NCT05850520

- Treatment related changes in circulating biomarkers (FBR)

Endpoints included in this application:

- Change from baseline in BCVA, measured by ETDRS letter score at week 36 and 64
- Proportion of participants losing ≥15 letters in BCVA from baseline at week 36 and week 64
- Change from baseline in CST at Weeks 36 and 64
- Change from baseline in NEI VFQ-25 total score at week 36
- TESAEs through weeks 36 and 64 (including intraocular inflammation)

Method of analysis

The primary estimand for the primary objective is described by the following attributes:

- Population: Adult participants with treatment-naïve macular edema secondary to RVO
- Endpoint: Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 36
- Treatment condition:
- Aflibercept 8 mg administered with 3 initial every 4 weeks (Q4W) initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
- Aflibercept 8 mg administered with 5 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
- Aflibercept 2 mg administered Q4W until Week 32, followed by adjustment of treatment intervals according to treatment response

A delayed active injection resulting in an injection interval up to 4 weeks longer than planned is considered to be in line with the treatment regimen of interest.

- Intercurrent events and strategies:
- Premature treatment discontinuation – addressed by the hypothetical strategy (had participants continued treatment until Week 36)
- Use of prohibited medication – addressed by the hypothetical strategy (had prohibited medications not been taken)
- Missed study intervention:

- Missed active injection resulting in an injection interval up to 4 weeks longer than planned: treatment policy strategy (the effect of a missed active injection will be included in the estimate of the treatment effect)
- Missed active injection resulting in an injection interval more than 4 weeks longer than planned: hypothetical strategy (had injection not been missed or delayed by less than 4 weeks)

- Population-level summary: Difference in mean change from baseline to Week 36 in BCVA between each aflibercept 8 mg group and the aflibercept 2 mg group.

Subgroup analyses	Exploratory subgroup analyses will be performed, using descriptive summary statistics for the following subgroups: 1. Age at enrollment: < 55 years, ≥ 55 to < 65 years, ≥ 65 years to < 75 years, ≥ 75 years 2. Sex: male, female 3. Geographic region: - Japan vs. APAC vs Europe vs America - USA vs Rest of the world - Asia (Japan and APAC) vs ROW 4. Ethnicity: Not Hispanic or Latino, Hispanic or Latino 5. Race (only categories with sufficient sample size): Asian, White 6. Baseline BCVA: < 60 letters, ≥ 60 letters 7. Baseline CST: ≤ observed median, > observed median 8. Medical history of hypertension: No, Yes (see section 6.3.1) 9. Medical history of diabetes: No, Yes 10. Medical history of cerebrovascular disease: No, Yes (see section 6.3.4) 11. Medical history of ischaemic heart disease: No, Yes (see section 6.3.5) 12. Medical history of renal impairment: Normal, Mild, Moderate, Severe (see section 6.3.6) 13. Medical history of hepatic impairment: No, Yes (see section 6.3.7)

	Subgroups 1 to 7 will be analyzed for the primary and key secondary endpoints. For subgroup analysis based on geographic regions and categorized baseline BCVA, the corresponding variable will be excluded from the statistical models. These subgroup analyses are exclusively descriptive, and tables will present 95% confidence intervals. For the primary endpoint, subgroups will be analyzed using the MMRM without imputing missing values (see Section 4.2.2), for the key-secondary endpoint, subgroups will be analyzed using the non-parametric rank ANCOVA (see Section 4.3.1.2). In the subgroup analyses of the key-secondary endpoint, the stratification factor "region" will be excluded from the analysis and imputation model to mitigate issues associated with small sample sizes within strata. Subgroups 1 to 13 will be analyzed for the safety analyses mentioned in Section 4.5.1.1. If the number of participants in a subgroup is less than 10%, the subgroup categories may be redefined prior to unmasking.
Other relevant information	Not applicable

Appendix B. Efficacy results per study

Table 29. Results per study

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in BCVA, measured by ETDRS letter score at:										The primary estimand for the primary objective is described by the following attributes: • Population: Adult participants with treatment-naïve macular edema secondary to RVO • Endpoint: Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 36 • Treatment condition: • Aflibercept 8 mg administered with 3 initial every 4 weeks (Q4W) initiation doses followed	
Week 36:											
	2 mg Q4W	301	17.5 (16.1-18.9)								
	8 mg Q8/3	293	17.4 (16.1-18.8)	-0.1	-2.0 - 1.9	0.5262					
	8 mg Q8/5	298	18.3 (17.0-19.5)	0.8	-1.1 – 2.7	0.2067					

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Week 64:	2 mg Q4W	301	17.3 (15.7-18.9)							by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response • Aflibercept 8 mg administered with 5 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response • Aflibercept 2 mg administered Q4W until Week 32, followed by adjustment of treatment intervals according to treatment response A delayed active injection resulting in an injection interval up to 4 weeks longer than planned is considered to be in line with the treatment regimen of interest.	
	8 mg Q8/3	293	17.8 (16.4-19.3)	0.5	-1.6 – 2.7	0.3198					
	8 mg Q8/5	298	18.1 (16.5-19.6)	0.7	-1.5 – 2.9	0.2597					

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										• Intercurrent events and strategies: • Premature treatment discontinuation – addressed by the hypothetical strategy (had participants continued treatment until Week 36) • Use of prohibited medication – addressed by the hypothetical strategy (had prohibited medications not been taken) • Missed study intervention: • Missed active injection resulting in an injection interval up to 4 weeks longer than planned: treatment policy strategy (the effect of a missed active injection will be included in the	

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										estimate of the treatment effect) • Missed active injection resulting in an injection interval more than 4 weeks longer than planned: hypothetical strategy (had injection not been missed or delayed by less than 4 weeks) • Population-level summary: Difference in mean change from baseline to Week 36 in BCVA between each aflibercept 8 mg group and the aflibercept 2 mg group.	

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of participants losing less than 15 letters in BCVA from baseline at										Proportion of participants losing less than 15 letters in BCVA from baseline summarized descriptively by treatment group for all observed cases until the occurrence of an ICE with imputation of missing values with LOCF in the FAS population.	
Week 36											
	2 mg Q4W	301	293 (97.3%) ((94.8% - 98.9%)								
	8 mg Q8/3	293	287 (98.0%) (95.6% - 99.2%)	0.6 %	-2.07% - 3.37%		1.0063	0.98 – 1.03			
	8 mg Q8/5	298	291 (97.7%) (95.2% - 99.1%)	0.3 %	-2.44% - 3.10%		1.0032	0.98 – 1.03			

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Week 64	2 mg Q4W	301	291 (96.7%) (94.0 % - 98.4%)								
	8 mg Q8/3	293	287 (98.0%) (95.6% - 99.2%)	1.3 %	-1.49% - 4.21%		1.0132	0.99 – 1.04			
	8 mg Q8/5	298	288 (96.6%) (93.9% - 98.4%)	-0.0 %	-3.15% - 3.06%		0.9997	0.97 – 1.03			
Change from baseline in National Eye Institute visual functioning questionnaire-25 – total score at										An analysis of covariance (ANCOVA) was used with baseline NEI-VFQ-25 total score measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs. >=60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors. Data after occurrence of an ICE was excluded in line with the sensitivity estimand strategy.	
week 36	2 mg Q4W	301	6.27 (4.96-7.58)								
	8 mg Q8/3	293	5.91 (4.71-7.11)	-0.36	-2.10 – 1.40	0.6869					

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	8 mg Q8/5	298	6.92 (5.69-8.15)	0.65	-1.20 – 2.45	0.4792					
Change in baseline Central subfield thickness (CST)										A mixed model for repeated measurements (MMRM) was used with baseline CST measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.>=60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors, and terms for the interaction between baseline CST and visit and treatment and visit. Covariance structure used: unstructured covariance structure. Intercurrent events were handled according to primary estimand strategy.	
Week 36											
	2 mg Q4W	301	-370.8 (-378.4; -363.2)								
	8 mg Q8/3	293	-370.9 (-376.0; -364.8)	-0.1	-10.0 – 9.8	0.9804					
	8 mg Q8/5	298	-369.5 (-374.0; -364.0)	1.2	-7.7 – 10.2	0.7863					

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Week 64	2 mg Q4W	301	-353.7 (-363.9; -343.5)								
	8 mg Q8/3	293	-361.1 (-369.5; -352.7)	-7.4	-20.7 – 5.9	0.2779					
	8 mg Q8/5	298	-353.3 (-361.3; -345.3)	0.5	-12.6 – 13.5	0.9455					

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Any TEAE of intraocular inflammation in the study eye										Proportion of participants with ocular treatment-emergent intraocular inflammation summarized descriptively by treatment group in the safety analysis set population.	
Week 36	2 mg Q4W	301	4 (1.3 %) (0.36% - 3.37%)								
	8 mg Q8/3	293	2 (0.7%) (0.08% - 2.44%)	-0.6%	-2.77%-1.27%		0.5137	0.09 – 2.78			
	8 mg Q8/5	298	1 (0.3%) (0.01% - 1.86%)	-1.0%	-3.07% - 0.67%		0.2525	0.03 – 2.25			
Week 64	2 mg Q4W	301	5 (1.7%) (0.54% - 3.83%)								

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	8 mg Q8/3	293	4 (1.4%) (0.37% - 3.46%)	-0.3%	-2.64% - 2.00%		0.8218	0.22 – 3.03			
	8 mg Q8/5	298	2 (0.7%) (0.08% - 2.40%)	-1.0%	-3.24% - 0.94%		0.4040	0.08 – 2.07			
Ocular TESAEs in study eye Week 36	2 mg Q4W	301	7 (2.3%) (0.94% - 4.73%)							Proportion of participants with ocular treatment-emergent serious adverse events summarized descriptively by treatment group in the safety analysis set population.	
	8 mg Q8/3	293	3 (1.0%) (0.21% - 2.96%)	-1.3%	-3.83% - 0.93%		0.4403	0.11 – 1.69			
	8 mg Q8/5	298	4 (1.3%) (0.37% - 3.40%)	-1.0%	-3.55% - 1.37%		0.5772	0.17 – 1.95			

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Week 64	2 mg Q4W	301	8 (2.7%) (1.15% - 5.17%)								
	8 mg Q8/3	293	5 (1.7%) (0.56% - 3.94%)	-1.0%	-3.66% - 1.61%		0.6421	0.21 – 1.94			
	8 mg Q8/5	298	5 (1.7%) (0.55% - 3.87%)	-1.0%	-3.69% - 1.54%		0.6313	0.21 – 1.91			
Non-ocular TESAE Week 36	2 mg Q4W	301	25 (8.3%) (5.45% - 12.02%)							Proportion of participants with non-ocular treatment-emergent serious adverse events summarized descriptively by treatment group in the safety analysis set population.	
	8 mg Q8/3	293	21 (7.2%) (4.49% - 10.75%)	-1.1%	-5.57% - 3.27%		0.8629	0.49 – 1.51			
	8 mg Q8/5	298	22 (7.4%)	-0.9%	-5.36% - 3.49%		0.8889	0.51 – 1.54			

Results of QUASAR Study NCT05850520											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
			(4.68% - 10.96%)								
Week 64	2 mg Q4W	301	36 (12.0%)								
			(8.52% - 16.17%)								
	8 mg Q8/3	293	33 (11.3%)	-0.7%	-5.92% - 4.54%		0.9417	0.60 – 1.47			
			(7.88% - 15.45%)								
	8 mg Q8/5	298	33 (11.1%)	-0.9%	-6.08% - 4.30%		0.9259	0.59 – 1.44			
			(7.75% - 15.20%)								

Appendix C. Comparative analysis of efficacy

Not relevant for this application

Table 30. Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Example:		NA	NA	NA	NA	NA	NA	NA	NA
Example:		NA	NA	NA	NA	NA	NA	NA	
Example:		NA	NA	NA	NA	NA	NA	NA	
Insert outcome 4									

Appendix D. Literature searches for the clinical assessment

D.1 Efficacy and safety of the intervention and comparator(s)

Not relevant for this application

Table 31. Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
NA	NA	NA	NA
NA	NA	NA	NA
NA	NA	NA	NA

Abbreviations:

Table 32. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA	NA	NA	NA
NA	NA	NA	NA

Abbreviations:

Table 33. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	NA
NA	NA	NA		NA

Abbreviations:

D.1.2 Search strategies

Not relevant for this application

Table 3 of search strategy table for [name of database]

No.	Query	Results
NA	NA	NA

No.	Query	Results
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA

D.1.3 Systematic selection of studies

Table 35. Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	NA	NA
Intervention	NA	NA
Comparators	NA	NA
Outcomes	NA	NA
Study design/publication type	NA	NA
Language restrictions	NA	NA

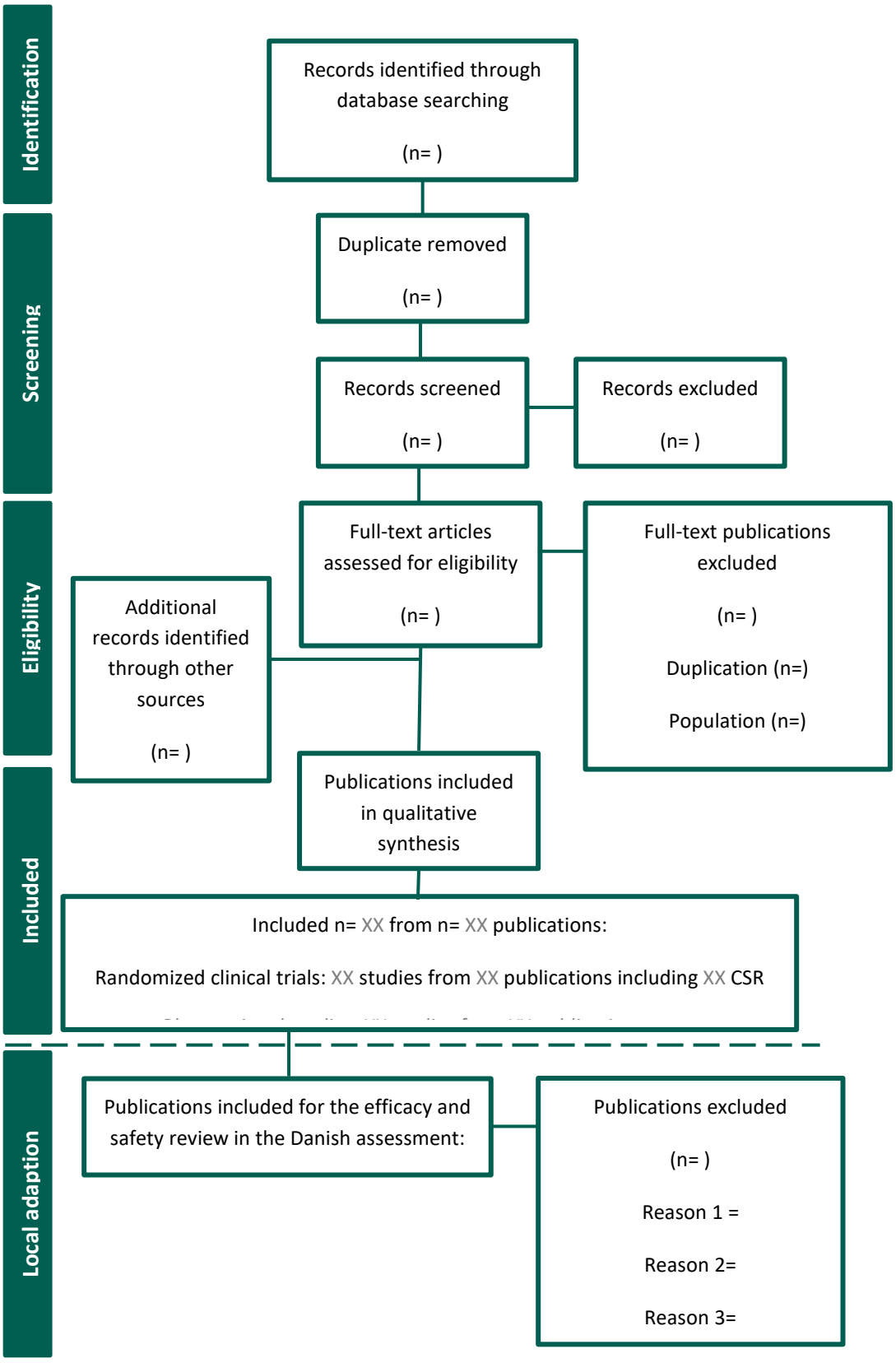
Table 36.4 Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	NA	NA	NA	NA	NA	NA
Study 2	NA	NA	NA	NA	NA	NA

D.1.4 Quality assessment

D.1.5 Unpublished data

Not relevant for the application



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