Medicinrådet

Bilag til direkte indplacering af aflibercept (8 mg dosering) i Medicinrådets behandlingsvejledning vedrørende lægemidler til våd aldersrelateret makuladenegeneration

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. aflibercept (8 mg dosering) til våd AMD
2. Ansøgers endelige ansøgning vedr. aflibercept (8 mg dosering) til våd AMD

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18.03.2024
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	April 2024
Leverandør	Bayer
Lægemiddel	Eylea (aflibercept)
Ansøgt indikation	Indplacering i behandlingsvejledning vedrørende lægemidler til våd aldersrelateret makuladegeneration (våd AMD)
Nyt lægemiddel/indikationsudvidelse	Ny styrke (direkte indplacering) – 8 mg

Prisinformation

Amgros har følgende aftalepris på Eylea (aflibercept):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP, (DKK)	Rabatprocent ift. AIP
Eylea (aflibercept)	114,3 mg/ml	Hætteglas Svarer til 0,07 ml (8 mg)	5.132,01	[redacted]	[redacted]
Eylea (aflibercept)	40 mg/ml	Hætteglas Svarer til 0,05 ml (2 mg)	5.132,01	[redacted]	[redacted]
Eylea (aflibercept)	40 mg/ml	Forfyldt sprøjte Svarer til 0,05 ml (2 mg)	5.132,01	[redacted]	[redacted]

Aftaleforhold

Eylea er en del af udbuddet, som er baseret på behandlingsvejledningerne indenfor våd AMD, diabetisk maculaødem (DME) og retinal veneokkusion (RVO). Den nye styrke 8 mg bliver direkte indplaceret i behandlingsvejledningerne for våd AMD og DME på lige fod med de andre lægemidler til disse indikationer. Aftalen gælder indtil den 31.12.2024 og kan forlænges med 2 gange 6 måneder.

Konkurrencesituationen

Der er i dag behandlingsvejledninger og lægemiddelrekommandationer for behandling af våd AMD og DME, hvor Lucentis (ranibizumab), Eylea (aflibercept) og Vabysmo (faricimab) er ligestillet til samme patient-population.
Vurderingsrapporten beskriver, at sammenligningen af aflibercept 2 mg og 8 mg, også kan anvendes til at konkludere på forholdet imellem Eylea 8 mg og øvrige lægemidler. Der vil blive udarbejdet en opdateret omkostningsanalyse på disse lægemidler ifm. indplacering af Eylea 8 mg.

Tabel 2: lægemiddeludgifter for Eylea 2 mg og 8 mg over 5,4 år (jf. Medicinrådets behandlingsvejledning)

Lægemiddel	Styrke	Pakkings-størrelse	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 5,4 år (SAIP, DKK)
Eylea	114,3 mg/ml	8 mg (hætteglas)	Gennemsnitligt 21,3 injektioner over 5,4 år. (fordelt på Q12W og Q16 W)	[redacted]	[redacted]
Eylea	40 mg/ml	2 mg (forfyldt sprøjte)	Gennemsnitligt 28,3 injektioner over 5,4 år	[redacted]	[redacted]
Eylea	40 mg/ml	2 mg (hætteglas)	Gennemsnitligt 28,3 injektioner over 5,4 år	[redacted]	[redacted]

*Udregninger i vurderingsrapporten afsnit 6.1.
**Inkluderer ikke eventuel vialsplitting hvis der anvendes hætteglas.

Status fra andre lande

Tabel 1: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til vurdering
England	Vurderes ikke i NICE	Godkendt i MHRA (UK medicines and Healthcare products regulatory agency)	Link til vurdering

Konklusion

[redacted]

Application for the assessment of aflibercept 8 mg by updating the “Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til våd aldersrelateret makuladegeneration (våd AMD)”

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Abbreviations

[Include a list of all abbreviations used in this application.]

AE	adverse event
AMD	age-related macular degeneration
BCVA	best corrected visual acuity
BMI	body mass index
CNV	choroidal neovascularisation
CST	central subfield retinal thickness
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAS	full analysis set
IRF	intraretinal fluid
logMAR	logarithm of the minimum angle of resolution
MoA	mechanism of action
nAMD	neovascular age-related macular degeneration
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
OCT	optical coherence tomography
OCT-A	optical coherence tomography–angiography
Q8W	every 8 weeks
Q12W	every 12 weeks
Q16W	every 16 weeks
QoL	quality of life
RCT	randomised controlled trial
RPE	retinal pigment epithelial
SRF	subretinal fluid
T&E	treat and extend regimen
VA	visual acuity
VEGF	vascular endothelial growth factor
µm	micrometres (microns)

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	Neovascular age related macula degeneration
Marketing authorization holder in Denmark	Bayer A/S
ATC code	S01LA05
Combination therapy and/or co-medication	None
(Expected) Date of EC approval	03-15 Jan 2024
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	Treatment of diabetic maculopathy – DME (8 mg)
Other indications that have been evaluated by the DMC (yes/no)	Ongoing evaluation of diabetic macula edema (8 mg) Diabetic macula edema (2 mg) (Approved) Neovascular age related macula degeneration (2 mg) (Approved) Retinal vein occlusion (2 mg) (Approved)
Dispensing group	NA
Packaging – types, sizes/number of units and concentrations	Package with 1 vial 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 neovascular (wet) age-related macular degeneration (nAMD)
Dosage regiment and administration:	Intravitreal injection of aflibercept 8 mg (0.07 ml) administered every 12 weeks (Q12W), after 3 initial injections at 4-week intervals. Intravitreal injection of aflibercept 8 mg (0.07 ml) administered every 16 weeks (Q16W), after 3 initial injections at 4-week intervals.
Choice of comparator [if any]	Intravitreal injection of aflibercept 2 mg (0.05 ml) administered every 8 weeks (Q8W), after 3 initial injections at 4-week intervals.
Most important efficacy endpoints (Difference/gain compared to comparator)	At week 48, aflibercept 8 mg administered in two extended dosing regimens (every 12 and 16 weeks) demonstrated non-inferiority on the primary endpoint of change in best corrected visual acuity (BCVA) compared with aflibercept 2 mg dosed every 8 weeks; this non-inferiority was maintained at week 60 and 96 o The primary analysis endpoint was met: treatment with aflibercept 8 mg every 12 and every 16 weeks demonstrated non-inferiority to aflibercept 2 mg, with mean changes in BCVA from baseline to week 48 of 6.06, 5.89, and 7.03 letters in the aflibercept 8 mg every 12 and 16 weeks and aflibercept 2 mg groups, respectively At week 16, aflibercept 8 mg administered in two extended dosing regimens (every 12 and 16 weeks) demonstrated superior fluid control, defined as no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the central subfield, compared with aflibercept 2 mg, indicating more rapid control of the disease. Superior fluid control was maintained through to week 48; at week 60, the effect was similar across all 3 treatment groups o At week 16, the proportion of patients with no IRF and no SRF in the central subfield was significantly higher in the aflibercept 8 mg pooled groups (63.3%) than the aflibercept 2 mg group (51.6%, p=0.0002) At week 48, 60 and 96, the proportion of patient losing ≥15 ETDRS letters were comparable between the dosing regimens with aflibercept 8 mg (every 12 or 16 weeks) and aflibercept 2 mg. At week 48, aflibercept 8 mg administered in two extended dosing regimens (every 12 and 16 weeks) demonstrated comparable efficacy to aflibercept 2 mg in terms of

Summary	
	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 in two extended dosing regimens (every 12 and 16 weeks) in the PULSAR 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 the 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 96 was similar across all 3 treatment groups (51.0% for aflibercept 8 mg Q12W, 53.3% for aflibercept 8 mg Q16W, and 53.9% for aflibercept 2 mg Q8W group) The proportion of patients with an ocular treatment-emergent serious adverse event (SAE) in the study eye was low in all treatment groups, and most of the ocular treatment-emergent SAEs in the study eye were reported in single participants in any treatment group through week 96 The rates of intraocular inflammation were 0.7% for aflibercept 8 mg and 1.2% for aflibercept 2 mg through week 96 There were no clinically relevant differences in intraocular pressure between the treatment groups through week 96 In the aflibercept 8 mg groups, there were no cases of endophthalmitis and no new safety signals through week 96

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 våd aldersrelateret makuladegeneration (våd AMD)”.

3.2 The intervention

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF (1). 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 (2,3) (Eylea 8 mg SmPC). This binding affinity is much higher than the native receptors, binding these proteins more strongly than ranibizumab, bevacizumab, or brolucizumab (3,4).

Aflibercept 2 mg is a widely established effective first-line treatment option for nAMD, broadly used in clinical practice and recommended in clinical guidelines (5,6,1). 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 is expected to improve patient adherence and, consequently short- and long-term visual outcomes in clinical practice.

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 (2). 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 (2) (Eylea 8 mg SmPC). PlGF binds only to VEGFR-1, which is also present on the surface of leukocytes (2). Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability (4). 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,

diabetic retinopathy (DR), diabetic macular oedema (DME), and retinal vein occlusion (RVO) (4) (Eylea 8 mg SmPC).

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 (6, 7)

- In animal models of CNV, blockade of VEGF signaling strongly suppresses the development of CNV, suggesting that VEGF is a necessary stimulus (8, 9)

- Likewise, VEGF blockade prevents or reverses neovascularisation in animal models of ischaemic retinopathy (9)

- In addition to VEGF itself, the related angiogenic protein, PlGF, has also been implicated in ocular neovascularisation (9)

Overview of intervention	
Therapeutic indication relevant for the assessment	Treatment of neovascular (wet) age-related macula degeneration (nAMD)
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 up to 16 weeks based on the physician's judgement of visual and/or anatomic outcomes. Subsequently, the treatment intervals may be further adjusted up to every 5 months (20 weeks), 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
Package size(s)	Package containing a single vial of aflibercept 8 mg (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 nAMD.

[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
PULSAR - NCT04423718 Not yet published in a scientific journal	Randomized, Double-Masked, Active-Controlled, Phase 3 Study	The ongoing masked part of the study (up to week 96) consists of a 3-week screening period, a treatment period of 92 weeks, and an end-of-study visit at week 96. An extension study with aflibercept 8 mg in all treatment groups starts immediately after the last scheduled procedure at the end of the week-96 study visit and consists of a transition period of 12 weeks (week 96 to week 108), during which the study drug is still administered in a masked fashion, followed by an open-label treatment period of 48 weeks, and an end-of-study visit at week 156.	Start: 11/08/20 Primary completion: 18/07/22 Study completion: 12/08/24	Treatment of naïve patients with neovascular age-related macula degeneration	Aflibercept 8 mg. Intravitreal administration. Dosing: Aflibercept 8 mg administered every 12 weeks (Q12W), after 3 initial injections at 4-week intervals Aflibercept 8 mg administered every 16 weeks (Q16W), after 3 initial injections at 4-week intervals	Aflibercept 2 mg. Intravitreal administration. Administered every 8 weeks (Q8W), after 3 initial injections at 4-week intervals	Not relevant	At week 48, aflibercept 8 mg administered in two extended dosing regimens (every 12 and 16 weeks) demonstrated non-inferiority on the primary endpoint of change in best corrected visual acuity (BCVA) compared with aflibercept 2 mg dosed every 8 weeks; this non-inferiority was maintained at week 60 and 96 At week 48, 60 and 96, the proportion of patient losing ≥15 ETDRS letters were comparable between the dosing regimens with aflibercept 8 mg (every 12 or 16 weeks) and aflibercept 2 mg. At week 48, aflibercept 8 mg administered in two extended dosing regimens (every 12 and 16 weeks) demonstrated comparable efficacy to aflibercept 2 mg in terms of improvement in vision-related quality

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
								of life, as measured by mean improvement in NEI VFQ-25 total score The safety of aflibercept 8 mg administered in two extended dosing regimens (every 12 and 16 weeks) in the PULSAR 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 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 #1: Is there any clinical significant difference between anti-VEGF agents for treatment of neovascular AMD?

5.1 Efficacy of aflibercept 8 mg compared to aflibercept 2 mg for neovascular AMD

5.1.1 Relevant studies

Overview of phase 3 PULSAR study design for aflibercept 8 mg in neovascular age-related macular degeneration

PULSAR is an ongoing phase 3, multicentre, randomised, double-masked, active-controlled study investigating the efficacy, safety, and tolerability of intravitreal administration of aflibercept 8 mg compared with aflibercept 2 mg in treatment-naïve patients with nAMD.

The primary objective of the study was to determine if treatment with aflibercept 8 mg at intervals of 12 or 16 weeks (both after 3 initial injections at 4-week intervals) provides non-inferior BCVA change compared with aflibercept 2 mg every 8 weeks (after 3 initial injections at 4-week intervals) in participants with nAMD. The secondary objectives were to determine the effect of aflibercept 8 mg versus 2 mg aflibercept on functional and anatomic measures of response as well as on vision-related quality of life and to evaluate the safety and tolerability of aflibercept 8 mg.

The ongoing masked part of the study (up to week 96) consists of a 3-week screening period, a treatment period of 92 weeks, and an end-of-study visit at week 96. An extension study with aflibercept 8 mg in all treatment groups starts immediately after the last scheduled procedure at the end of the week-96 study visit and consists of a transition period of 12 weeks (week 96 to week 108), during which the study drug is still administered in a masked fashion, followed by an open-label treatment period of 48 weeks, and an end-of-study visit at week 156.

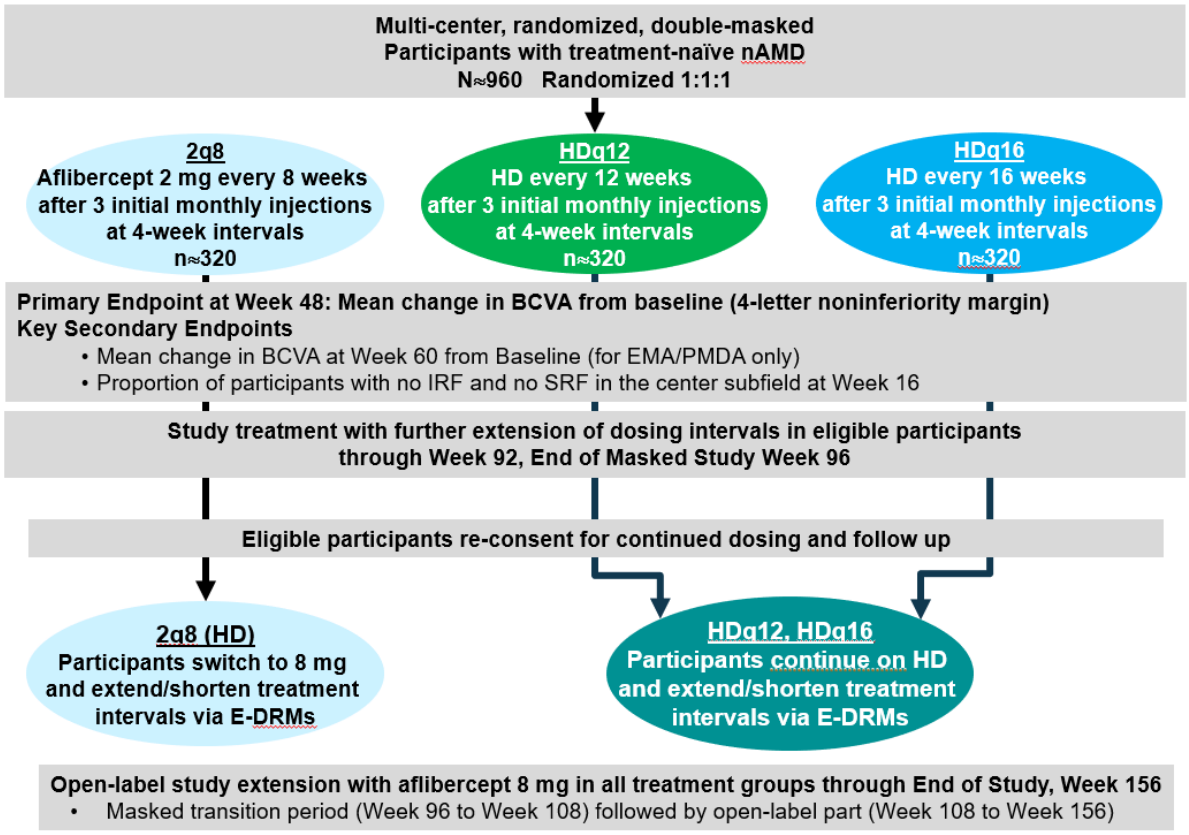
The study is being conducted at 251 sites in 27 countries or regions in Europe, North America, Latin America, Australia, and Asia Pacific. Of the total sample size of approximately 960 participants, at least 96 (10%) were planned to be enrolled in Japan to provide consistent results with a certain probability as required by Japanese Pharmaceuticals and Medical Devices Agency (PMDA) guidelines.

Participants were randomly assigned in a 1:1:1 ratio to 1 of 3 parallel treatment groups:

- Aflibercept 2 mg administered every 8 weeks (Q8W), after 3 initial injections at 4-week intervals

- Aflibercept 8 mg administered every 12 weeks (Q12W), after 3 initial injections at 4-week intervals
- Aflibercept 8 mg administered every 16 weeks (Q16W), after 3 initial injections at 4-week intervals

Figure 1 PULSAR study design overview



Q8W=aflibercept 2 mg every 8 weeks (Q8W); BCVA=best corrected visual acuity; E-DRM=dose regimen modification criteria for extension period; EMA=European Medicines Agency; HD=high dose (i.e., aflibercept 8 mg); IRF=intraretinal fluid; N=total number of participants; n=number of participants per group; nAMD=neovascular (wet) age-related macular degeneration; PMDA=Pharmaceuticals and Medical Devices Agency; SRF=subretinal fluid; q12=every 12 weeks (Q12W); q16=every 16 weeks (Q16W)

Source: PULSAR Clinical Study Protocol.

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 PULSAR study: Demographics and baseline disease characteristics

	Aflibercept 2 mg Q8W	Aflibercept 8 mg Q12W	Aflibercept 8 mg Q16W	Pooled
Sex, n (%)				
Female	188 (56.0%)	182 (54.3%)	180 (53.3%)	362 (53.8%)
Male	148 (44.0%)	153 (45.7%)	158 (46.7%)	311 (46.2%)
Race, n (%)				
Asian	83 (24.7%)	74 (22.1%)	77 (22.8%)	151 (22.4%)
Asian Indian	0	0	0	0
Chinese	40 (11.9%)	31 (9.3%)	31 (9.2%)	62 (9.2%)
Japanese	34 (10.1%)	31 (9.3%)	33 (9.8%)	64 (9.5%)
Korean	9 (2.7%)	11 (3.3%)	12 (3.6%)	23 (3.4%)
Thai	0	0	0	0
Other	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Black or African American	2 (0.6%)	2 (0.6%)	0	2 (0.3%)
White	249 (74.1%)	256 (76.4%)	260 (76.9%)	516 (76.7%)
Not reported	2 (0.6%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
Multiple	0	1 (0.3%)	0	1 (0.1%)
Ethnicity, n (%)				
Hispanic or Latino	12 (3.6%)	7 (2.1%)	9 (2.7%)	16 (2.4%)
Not Hispanic or Latino	322 (95.8%)	322 (96.1%)	326 (96.4%)	648 (96.3%)
Not reported	2 (0.6%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Age, years				
Mean (SD)	74.2 (8.8)	74.7 (7.9)	74.5 (8.5)	74.6 (8.2)
Median	74.0	75.0	75.0	75.0
Min, max	50,96	52,93	53,95	52,95

	Aflibercept 2 mg Q8W	Aflibercept 8 mg Q12W	Q16W	Pooled
Age group, years, n (%)				
<65	45 (13.4%)	26 (7.8%)	43 (12.7%)	69 (10.3%)
≥65 to <75	126 (37.5%)	137 (40.9%)	124 (36.7%)	261 (38.8%)
≥75 to <80	69 (20.5%)	77 (23.0%)	66 (19.5%)	143 (21.2%)
≥80 to <85	59 (17.6%)	59 (17.6%)	66 (19.5%)	125 (18.6%)
≥85	37 (11.0%)	36 (10.7%)	39 (11.5%)	75 (11.1%)
Body mass index, kg/m²				
n	332	333	334	667
Mean (SD)	27.97 (5.15)	27.71 (5.28)	27.26 (5.00)	27.48 (5.14)
Median	27.00	27.10	26.25	26.60
Min, max	18.8, 44.3	16.0, 48.3	17.3, 53.5	16.0, 53.5
Systolic blood pressure, mm Hg				
n	336	335	338	673
Mean (SD)	133.08 (13.14)	134.06 (12.25)	133.70 (12.96)	133.88 (12.61)
Median	132.75	134.50	134.50	134.50
Min, max	97.5, 169.5	89.5, 175.5	92.5, 181.0	89.5, 181.0
Diastolic blood pressure, mm Hg				
n	336	335	338	673
Mean (SD)	75.89 (9.11)	75.95 (8.46)	77.01 (8.58)	76.48 (8.53)
Median	76.50	76.50	78.00	77.00
Min, max	52.0, 94.0	50.5,93.5	52.5,97.0	50.5,97.0
Heart rate, bpm				
n	336	335	338	673
Mean (SD)	71.6 (10.8)	72.1 (9.9)	71.8 (10.1)	72.0 (10.0)

	Aflibercept 2 mg Q8W	Aflibercept 8 mg Q12W	Q16W	Pooled
Median	71.0	72.0	71.0	72.0
Min, max	40, 115	46, 104	46, 111	46, 111
Fellow eye with history of nAMD, n (%)				
No	321 (95.5%)	324 (96.7%)	326 (96.4%)	650 (96.6%)
Yes	15 (4.5%)	11 (3.3%)	12 (3.6%)	23 (3.4%)
Prior fellow eye treatment, n (%)				
No	325 (96.7%)	329 (98.2%)	330 (97.6%)	659 (97.9%)
Yes	11 (3.3%)	6 (1.8%)	8 (2.4%)	14 (2.1%)
Aflibercept, n (%)	10 (3.0%)	3 (0.9%)	7 (2.1%)	10 (1.5%)
Bevacizumab, n (%)	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Ranibizumab, n (%)	2 (0.6%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Conberceptb, n (%)	0	1 (0.3%)	0	1 (0.1%)
Hypertension, n (%)				
No	132 (39.3%)	113 (33.7%)	119 (35.2%)	232 (34.5%)
Yes	204 (60.7%)	222 (66.3%)	219 (64.8%)	441 (65.5%)
Medical history of cerebrovascular disease, n (%)				
No	303 (90.2%)	304 (90.7%)	310 (91.7%)	614 (91.2%)
Yes	33 (9.8%)	31 (9.3%)	28 (8.3%)	59 (8.8%)
Medical history of ischaemic heart disease, n (%)				
No	289 (86.0%)	278 (83.0%)	300 (88.8%)	578 (85.9%)
Yes	47 (14.0%)	57 (17.0%)	38 (11.2%)	95 (14.1%)
Medical history of renal impairment, n (%)				
Normal	110 (32.7%)	99 (29.6%)	119 (35.2%)	218 (32.4%)
Mild	170 (50.6%)	172 (51.3%)	151 (44.7%)	323 (48.0%)

	Aflibercept 2 mg Q8W	Aflibercept 8 mg Q12W	Q16W	Pooled
Moderate	45 (13.4%)	54 (16.1%)	56 (16.6%)	110 (16.3%)
Severe	0	0	0	0
Missing	11 (3.3%)	10 (3.0%)	12 (3.6%)	22 (3.3%)
Medical history of hepatic impairment, n (%)				
No	322 (95.8%)	319 (95.2%)	323 (95.6%)	642 (95.4%)
Yes	14 (4.2%)	16 (4.8%)	15 (4.4%)	31 (4.6%)

bpm=beats per minute; nAMD=neovascular (wet) age-related macular degeneration; SD=standard deviation.

[a]Prior fellow eye treatment: refers to commercial aflibercept, bevacizumab, brolucizumab, ranibizumab, conbercept, pegaptanib sodium, or faricimab.

[b]Conbercept is an anti-VEGF therapy approved in China, currently not approved in the European Union,, United Kingdom, United States, Australia, or Canada.

Source: PULSAR Clinical Study Report (week 60).

Table 3 PULSAR study: Baseline disease characteristics of the study eye

	Aflibercept 2 mg Q8W	Aflibercept 8 mg Q12W	Aflibercept 8 mg Q16W	Pooled
BCVA, ETDRS letters score				
n	336	335	338	673
Mean (SD)	58.9 (14.0)	59.9 (13.4)	60.0 (12.4)	59.9 (12.9)
Median	62.0	62.0	61.0	62.0
Min, max	24,78	24,78	24,78	24,78
Categorized BCVA, ETDRS letters score, n (%)				
≤ 73	287 (85.4%)	293 (87.5%)	290 (85.8%)	583 (86.6%)
> 73	49 (14.6%)	42 (12.5%)	48 (14.2%)	90 (13.4%)
Categorized BCVA, ETDRS letters score[a], n (%)				
< 60	136 (40.5%)	141 (42.1%)	144 (42.6%)	285 (42.3%)
≥ 60	200 (59.5%)	194 (57.9%)	194 (57.4%)	388 (57.7%)
Intraocular pressure, mm Hg				
n	336	335	338	673
Mean (SD)	14.8 (3.0)	14.9 (3.2)	14.9 (3.2)	14.9 (3.2)
Median	15.0	15.0	15.0	15.0
Min, max	6, 25	7, 25	7, 25	7, 25
Geographic atrophy as per reading centre, n (%)				
No	328 (97.6%)	326 (97.3%)	326 (96.4%)	652 (96.9%)
Yes	3 (0.9%)	3 (0.9%)	6 (1.8%)	9 (1.3%)
Not available	5 (1.5%)	6 (1.8%)	6 (1.8%)	12 (1.8%)
Polypoidal choroidal vascularisation as per reading centre[b], n (%)				
No	53 (15.8%)	54 (16.1%)	46 (13.6%)	100 (14.9%)
Yes	54 (16.1%)	45 (13.4%)	42 (12.4%)	87 (12.9%)

	Aflibercept 2 mg Q8W	Aflibercept 8 mg Q12W	Q16W	Pooled
Not available	1 (0.3%)	2 (0.6%)	0	2 (0.3%)
Missing	228 (67.9%)	234 (69.9%)	250 (74.0%)	484 (71.9%)
Central subfield retinal thickness, as per reading centre, µm,				
n	335	335	336	671
Mean (SD)	367.1 (133.6)	370.3 (123.7)	370.7 (132.7)	370.5 (128.2)
Median	343.0	348.0	340.0	345.0
Min, max	142, 1116	151, 840	144, 913	144, 913
Choroidal neovascularisation size, as per reading centre, mm²				
n	336	335	337	672
Mean (SD)	6.3593 (5.0394)	5.9768 (4.8306)	6.5459 (5.5315)	6.2622 (5.1979)
Median	4.9970	4.8990	4.6980	4.8660
Min, max	0.148, 24.129	0.115, 30.023	0.000, 28.650	0.000, 30.023
Total lesion area, as per reading centre, mm²				
n	336	335	336	671
Mean (SD)	6.8647 (5.4145)	6.3820 (5.0664)	6.8814 (5.6514)	6.6321 (5.3691)
Median	5.4120	5.0260	5.0685	5.0320
Min, Max	0.148,27.409	0.185,30.023	0.180,28.650	0.180,30.023
Choroidal neovascularisation type, as per reading centre, n (%)				
Type 1 - occult or PCV	194 (57.7%)	198 (59.1%)	191 (56.5%)	389 (57.8%)
Type 2 - classic CNV	66 (19.6%)	68 (20.3%)	61 (18.0%)	129 (19.2%)
Type 1 and Type 2 - both classic and occult are present	66 (19.6%)	59 (17.6%)	74 (21.9%)	133 (19.8%)
Type 3 - RAP	5 (1.5%)	4 (1.2%)	5 (1.5%)	9 (1.3%)
Cannot grade	0	0	1 (0.3%)	1 (0.1%)

	Aflibercept 2 mg Q8W	Aflibercept 8 mg Q12W	Aflibercept 8 mg Q16W	Pooled
Not applicable - no CNV present	5 (1.5%)	6 (1.8%)	6 (1.8%)	12 (1.8%)
Choroidal neovascularisation classification, as per reading centre[c], n (%)				
CNV <50% of lesion	0	0	2 (0.6%)	2 (0.3%)
Predominantly classic	71 (21.1%)	71 (21.2%)	67 (19.8%)	138 (20.5%)
Minimally classic	61 (18.2%)	56 (16.7%)	68 (20.1%)	124 (18.4%)
Occult only	192 (57.1%)	197 (58.8%)	186 (55.0%)	383 (56.9%)
RAP	5 (1.5%)	4 (1.2%)	5 (1.5%)	9 (1.3%)
PCV	2 (0.6%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Cannot grade	0	0	1 (0.3%)	1 (0.1%)
Not applicable	5 (1.5%)	6 (1.8%)	6 (1.8%)	12 (1.8%)
NEI VFQ-25 total score				
n	317	321	316	637
Mean (SD)	77.8082 (14.4206)	76.3575 (15.1213)	77.6670 (15.3980)	77.0071 (15.2613)
Median	80.4545	79.5076	81.8485	80.6439
Min, max	36.9167, 99.4318	24.2083, 98.1818	16.1667, 98.1818	16.1667, 98.1818

BCVA=best corrected visual acuity; CNV=choroidal neovascularisation; CRF=case report form; ETDRS=Early Treatment Diabetic Retinopathy Study; FA=fluorescein angiography; FP=fundus photography; ICGA=indocyanine green angiography; IXRS=Interactive Response System; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25; PCV=polypoidal choroidal vascularisation; RAP=retinal angiomatous proliferation; SD=standard deviation.

[a]Baseline categories per CRF used for analyses; 16 participants in the full analysis set were stratified differently, based on the site's data entry into IXRS at the screening visit.

[b]PCV was diagnosed and characterized by ICGA measurements, which were optional and performed only at sites with the appropriate equipment.

[c]CNV was evaluated using FA/FP.

Source: PULSAR Clinical Study Report (week 60)

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

PULSAR study: Patient disposition

The disposition of patients in PULSAR is described in Table 4. There were 1395 enrolled patients, of whom 383 did not complete screening. From the enrolled patients, 1011 were randomised and 1009 patients were treated (FAS and SAF). Of these, 937 patients completed study treatment phase through week 48 and 925 patients through week 60.

Table 4 PULSAR study: Patient disposition through week 60

	Aflibercept 2 mg Q8W (n=337)	Aflibercept 8 mg Q12W (n=336)	Aflibercept 8 mg Q16W (n=338)	Aflibercept 8 mg Pooled (n=674)	Total (n=1011)
Week 48					
Number of patients who completed week 48	309 (91.7%)	316 (94.0%)	312 (92.3%)	628 (93.2%)	937 (92.7%)
Number of patients who discontinued prior to week 48	25 (7.4%)	18 (5.4%)	25 (7.4%)	43 (6.4%)	68 (6.7%)
Number of patients with unknown data, whether they completed the study by week 48	3 (0.9%)	2 (0.6%)	1 (0.3%)	3 (0.4%)	6 (0.6%)
Reasons for discontinuation prior to week 48					
Adverse event	5 (1.5%)	1 (0.3%)	5 (1.5%)	6 (0.9%)	11 (1.1%)
Physician decision	1 (0.3%)	3 (0.9%)	2 (0.6%)	5 (0.7%)	6 (0.6%)
Protocol deviation	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.2%)
Lost to follow-up	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Lack of efficacy	2 (0.6%)	0	0	0	2 (0.2%)
Withdrawal by subject	5 (1.5%)	5 (1.5%)	12 (3.6%)	17 (2.5%)	22 (2.2%)
Death	5 (1.5%)	3 (0.9%)	1 (0.3%)	4 (0.6%)	9 (0.9%)
Other	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	8 (0.8%)
COVID-19 pandemic	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (0.6%)
Week 60					
Number of patients who completed week 60	305 (90.5%)	310 (92.3%)	308 (91.1%)	618 (91.7%)	923 (91.3%)
Number of patients who discontinued prior to week 60	29 (8.6%)	23 (6.8%)	29 (8.6%)	52 (7.7%)	81 (8.0%)

	Aflibercept 2 mg Q8W (n=337)	Aflibercept 8 mg Q12W (n=336)	Aflibercept 8 mg Q16W (n=338)	Aflibercept 8 mg Pooled (n=674)	Total (n=1011)
Number of patients with unknown data, whether they completed the study by week 60	3 (0.9%)	3 (0.9%)	1 (0.3%)	4 (0.6%)	7 (0.7%)
Reasons for discontinuation prior to week 60					
Adverse event	6 (1.8%)	2 (0.6%)	5 (1.5%)	7 (1.0%)	13 (1.3%)
Physician decision	1 (0.3%)	4 (1.2%)	1 (0.3%)	5 (0.7%)	6 (0.6%)
Protocol deviation	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.2%)
Lost to follow-up	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.4%)	4 (0.4%)
Lack of efficacy	2 (0.6%)	0	0	0	2 (0.2%)
Withdrawal by subject	6 (1.8%)	8 (2.4%)	14 (4.1%)	22 (3.3%)	28 (2.8%)
Death	5 (1.5%)	3 (0.9%)	2 (0.6%)	5 (0.7%)	10 (1.0%)
Other	6 (1.8%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	10 (1.0%)
COVID-19 pandemic	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (0.6%)

COVID-19=Coronavirus disease 2019; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

Source: PULSAR Clinical Study Report (week 60).

Clinical efficacy from PULSAR study: Results at 48 weeks

Primary endpoint: Mean change in best corrected visual acuity as measured by the Early Treatment Diabetic Retinopathy Study letter score for aflibercept 8 mg (Q12W and Q16W) were non-inferior to aflibercept 2 mg at week 48

The PULSAR study found that aflibercept 8 mg administered Q12W or Q16W was non-inferior to aflibercept 2 mg injected Q8W in terms of least-squares (LS) mean improvement from BCVA as measured by ETDRS letter score at week 48 (Figure 6). The primary analysis of the change from baseline in BCVA resulted in LS mean changes from baseline to week 48 of 7.03 letters in the aflibercept 2 mg Q8W group compared with 6.06 letters in the aflibercept 8 mg Q12W group (p=0.0009 for non-inferiority versus aflibercept 2 mg Q8W group) and 5.89 letters in the aflibercept 8 mg Q16W group (p=0.0011 for non-inferiority versus aflibercept 2 mg Q8W group).

Non-inferiority to aflibercept 2 mg Q8W was maintained at week 60 for both aflibercept 8 mg dosing schedules, the key secondary efficacy endpoint.

The results of the primary analysis in the FAS population are supported by the corresponding results for the PPS population and all subgroup and sensitivity analyses; for more details, see the PULSAR Clinical Study Report (week 60).

Table 5 Change from baseline in BCVA measured by ETDRS letter score at week 48

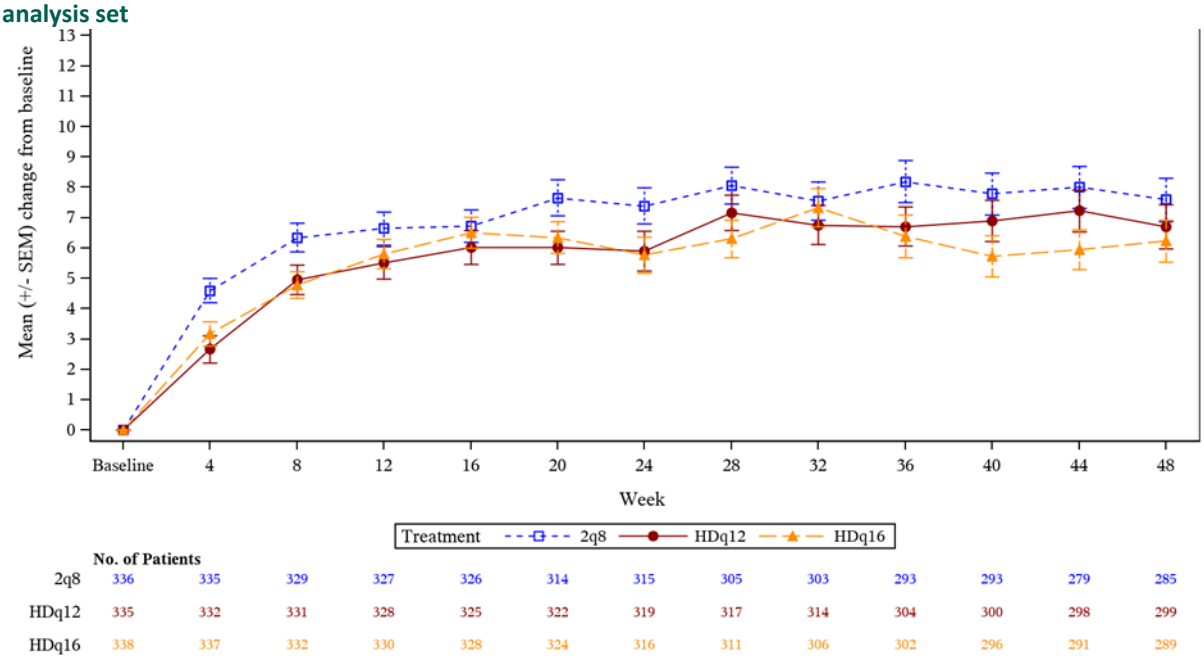
Full analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Aflibercept 8 mg Q16W n=338
Number of patients with week 48 data	285	299	289
Baseline mean	58.9	59.9	60.0
Arithmetic mean (SD) change from baseline	7.6 (12.2)	6.7 (12.6)	6.2 (11.7)
LS mean (SE) change from baseline	7.03 (0.74)	6.06 (0.77)	5.89 (0.72)
p value of 1-sided test for non-inferiority at a margin of 4 letters	-	0.0009	0.0011
Difference in LS mean versus aflibercept 2 mg Q8W (95% CI)	-	-0.97 (-2.87 to 0.92)	-1.14 (-2.97 to 0.69)

CI=confidence interval; LS=least squares; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; SD=standard deviation; SE=standard error.

Source: PULSAR Clinical Study Report (week 60).

Both arithmetic mean changes and LS mean changes from baseline in BCVA measured by the ETDRS letter score by visit were similar across aflibercept 2 mg Q8W, aflibercept 8 mg Q12W, and aflibercept 8 mg Q16W treatment groups, with minor numerical differences but not considered clinically relevant, demonstrating robustness of results on the primary endpoint. (Figure 2 and Figure 3)

Figure 2: Mean change from baseline in BCVA by visit, observed cases prior to intercurrent event: Full analysis set

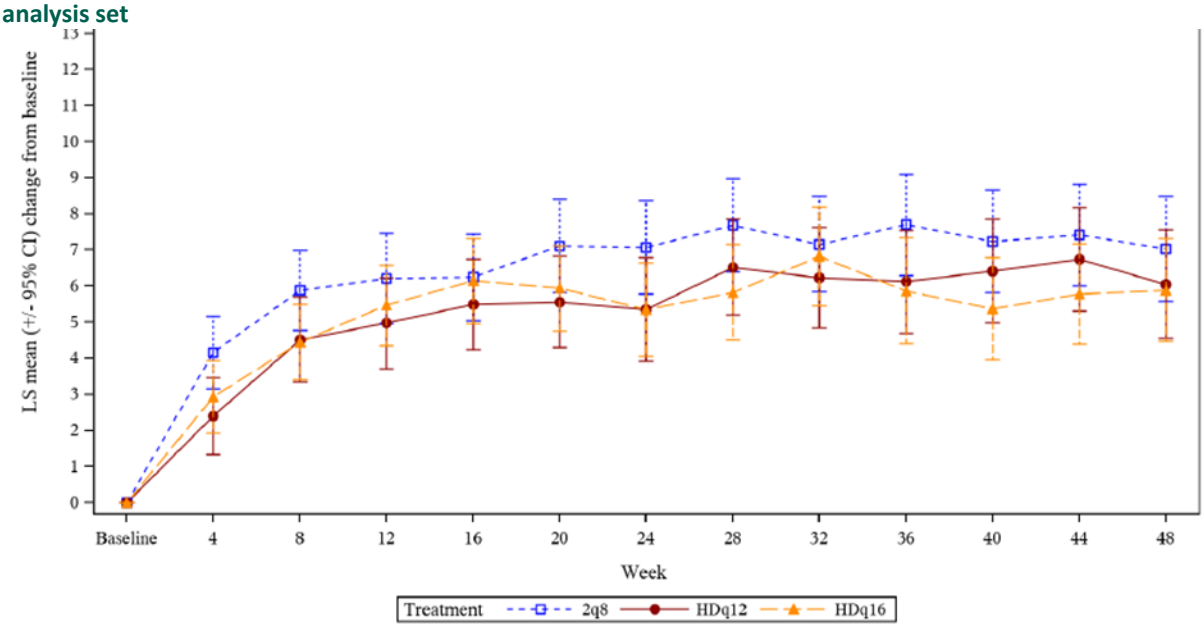


No. of Patients													
2q8	336	335	329	327	326	314	315	305	303	293	293	279	285
HDq12	335	332	331	328	325	322	319	317	314	304	300	298	299
HDq16	338	337	332	330	328	324	316	311	306	302	296	291	289

Q8W=aflibercept 2 mg every 8 weeks (Q8W); HD=high dose (i.e., aflibercept 8 mg); q12=every 12 weeks (Q12W); q16=every 16 weeks (Q16W); SEM=standard error of the mean.

Source: PULSAR Clinical Study Report (week 48).

Figure 3: Least-squares mean change from baseline in BCVA by visit, mixed model for repeat errors: Full analysis set



Q8W=aflibercept 2 mg every 8 weeks (Q8W); CI=confidence interval; HD=high dose (i.e., aflibercept 8 mg); LS=least squares; q12=every 12 weeks (Q12W); q16=every 16 weeks (Q16W); SEM=standard error of the LS mean.

Source: PULSAR Clinical Study Report (week 48).

Proportion of patients losing ≥15 letters at week 48 were comparable between 8 mg dosing groups and the group treated with aflibercept 2 mg

The proportion of participants who lost ≥15 letters in BCVA from baseline at week 48 was <6% in all 3 treatment groups, with only small numerical differences between the groups.

Table 6 Proportion of participants losing ≥15 letters in BCVA from baseline at week 48

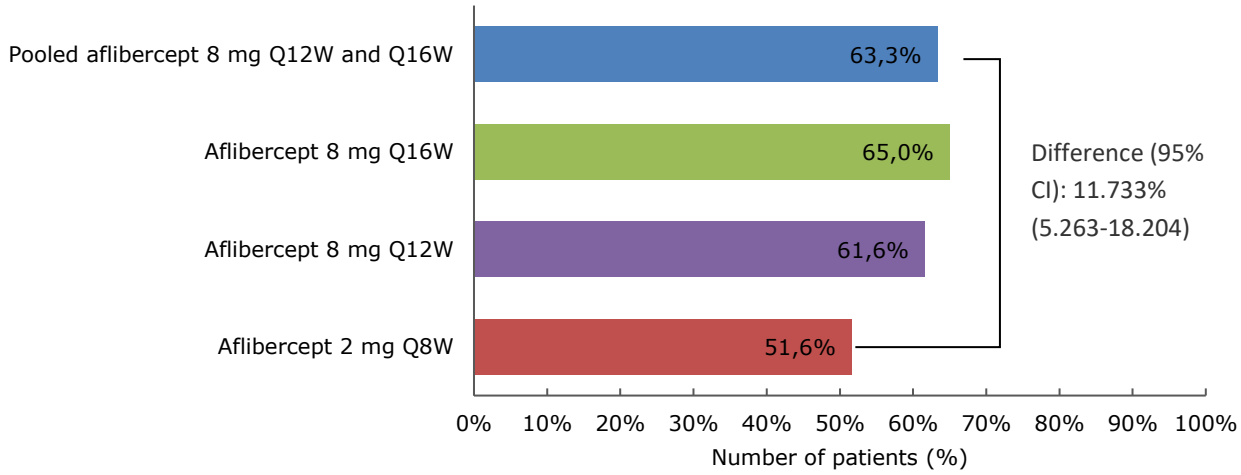
Exploratory endpoints through week 48, full analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg	
		Q12W n=335	Q16W n=338
Proportion of participants	N=335	N=334	N=337
▪ Gained ≥10 letters in BCVA	42.4%	38.9%	38.6%
▪ Gained ≥5 letters in BCVA	63.6%	55.7%	58.2%
▪ Lost ≥15 letters in BCVA	4.2%	5.4%	5.3%
▪ Lost ≥10 letters in BCVA	11.0%	13.2%	14.2%
▪ Lost ≥5 letters in BCVA	6.3%	8.1%	9.2%

Source: PULSAR Clinical Study Report (week 60).

Proportion of participants with no intraretinal fluid and no subretinal fluid in the central subfield at week 16 were significantly higher in patients treated with aflibercept 8 mg

The pooled analysis for proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the central subfield at week 16 was performed to determine the effect of the aflibercept 8 mg groups (Q12W and Q16W) compared with the aflibercept 2 mg Q8W group on this secondary endpoint. The proportion of participants with no IRF and no SRF in central subfield at week 16 was significantly higher in the aflibercept 8 mg groups (pooled Q12W and Q16W treatment groups) than in the aflibercept 2 mg Q8W group (63.3% versus 51.6%; p=0.0002) (Figure 4), indicating a more rapid disease control with aflibercept 8 mg. The difference (95% confidence interval [CI]) between pooled aflibercept 8 mg Q12W and Q16W treatment groups vs aflibercept 2 mg Q8W treatment was 11.7% points.

Figure 4 Proportion of patients with no IRF and no SRF in the central subfield at week 16



IRF=intraretinal fluid; SRF=subretinal fluid; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

Source: PULSAR Clinical Study Report (week 60).

Change from baseline in the National Eye Institute Visual Functioning Questionnaire-25 total score at week 48 for aflibercept 8 mg (Q12W and Q16W) were non-inferior to aflibercept 2 mg

The PULSAR study demonstrates that aflibercept 8 mg Q12W and Q16W treatment groups provides comparable efficacy to aflibercept 2 mg Q8W in terms of improvement in vision-related quality of life as measured by the NEI VFQ-25 questionnaire at week 48. The mean values of the NEI VFQ-25 total score at baseline (**Table 7Fejl! Henvisningskilde ikke fundet.**) were similar across the aflibercept 2 mg Q8W and aflibercept 8 mg Q12W and Q16W treatment groups and ranged from 76.4 to 77.8. The LS mean changes in the NEI VFQ-25 total score at week 48 (**Table 7Fejl! Henvisningskilde ikke fundet.**) were 3.50 in the aflibercept 8 mg Q12W group, 3.35 in the aflibercept 8 mg Q16W group, and 4.22 in the aflibercept 2 mg Q8W group, respectively.

Table 7: Change from baseline in NEI-VFQ-25 total score at week 48

Full analysis set	Aflibercept 2 mg	Aflibercept 8 mg	
	Q8W	Q12W	Q16W
	n=336	n=335	n=338
Number of patients with week 48 data	266	285	266
Baseline mean	77.8	76.4	77.7
Arithmetic mean (SD) change from baseline	4.6 (11.0)	4.1 (10.4)	3.4 (10.8)
LS mean (SE) change from baseline	4.22 (0.70)	3.50 (0.70)	3.35 (0.72)
p value for the 2-sided test	-	0.3817	0.3070
Difference in LS mean vs aflibercept 2 mg Q8W (95% CI)	-	-0.72 (-2.35 to 0.90)	-0.87 (-2.55 to 0.80)

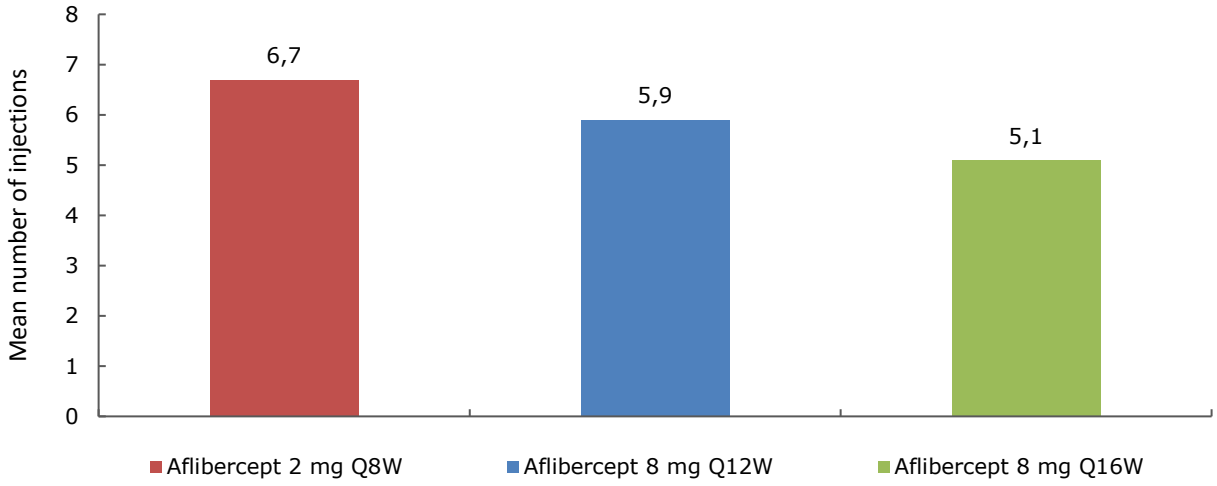
CI=confidence interval; LS=least squares; NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire25; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; SD=standard deviation; SE=standard error.

Source: PULSAR Clinical Study Report (week 60).

Mean number of injections at week 48 were numerical lower for patients treated with aflibercept 8 mg

Over the 48-week period, patients treated with aflibercept 8 mg received fewer injections compared with aflibercept 2 mg. The mean number of injections over 48 weeks was 5.9 in the aflibercept 8 mg Q12W group, 5.1 in the aflibercept 8 mg Q16W group and 6.7 in the aflibercept 2 mg Q8W group (**Figure** 5).

Figure 5: Mean number of aflibercept injections through week 48



Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

Source: PULSAR Clinical Study Report (week 60).

Aflibercept 8 mg demonstrated longer duration as a high number of patients were maintained on the initial assigned dosing interval

Maintenance of dosing interval with aflibercept 8 mg after 3 loading doses

Proportion of participants maintained with Q16W treatment interval through week 48 in the Q16W group

The majority of patients from aflibercept 8 mg Q16W group (76.6%) were maintained on the assigned dosing interval through week 48 (Table 8).

Proportion of participants maintained with Q12W or longer interval through week 48 in the Q12W and Q16W groups

The majority of patients from the aflibercept 8 mg Q12W group (79.4%) and Q16W group (87.2%) were maintained on Q12W or longer dosing interval through week 48. In the pooled aflibercept 8 mg groups, substantial majority (83.3%) of patients maintained Q12W or longer dosing interval through week 48 (Table 8).

Proportion of participants maintained with Q12W or Q16W interval as the last treatment interval at week 48 in the Q12W and Q16W groups, respectively

The proportion of participants with Q12W or longer treatment interval as the last treatment interval at week 48 was 79.4% in the aflibercept 8 mg Q12W and 86.9% in the Q16W group, and it was 83.1% in the pooled aflibercept 8 mg groups. The proportion of participants with Q16W or longer treatment interval as the last treatment interval at week 48 was 76.6% in the aflibercept 8 mg Q16W group (Table 8).

Table 8 Exposure to study treatment through week 48: Dosing intervals

n (%)	Aflibercept 8 mg		
	Q12W n=335	Q16W n=338	Pooled n=628
Patients maintained with Q12W or longer dosing interval	251 (79.4%)	272 (87.2%)	523 (83.3%)
Patients maintained with Q16W dosing interval	-	239 (76.6%)	-
Patients with Q12W or longer dosing interval as the last intended dosing interval	251 (79.4%)	271 (86.9%)	522 (83.1%)
Patients with Q16W dosing interval as the last intended dosing interval	-	239 (76.6%)	-
Patients shortened to Q8W dosing interval at week 16	17 (5.4%)	10 (3.2%)	27 (4.3%)
Patients shortened to Q8W dosing interval at week 20	25 (7.9%)	21 (6.7%)	46 (7.3%)
Patients shortened anytime	65 (20.6%)	73 (23.4%)	138 (22.0%)
Patients shortened to Q8W dosing interval anytime	65 (20.6%)	40 (12.8%)	105 (16.7%)
Patients shortened to Q12W dosing interval anytime	-	33 (10.6%)	-

Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

Source: PULSAR Clinical Study Report (week 60).

Clinical efficacy from PULSAR study: Week 60 results

The efficacy demonstrated at week 48 in both aflibercept 8 mg treatment groups was maintained at week 60.

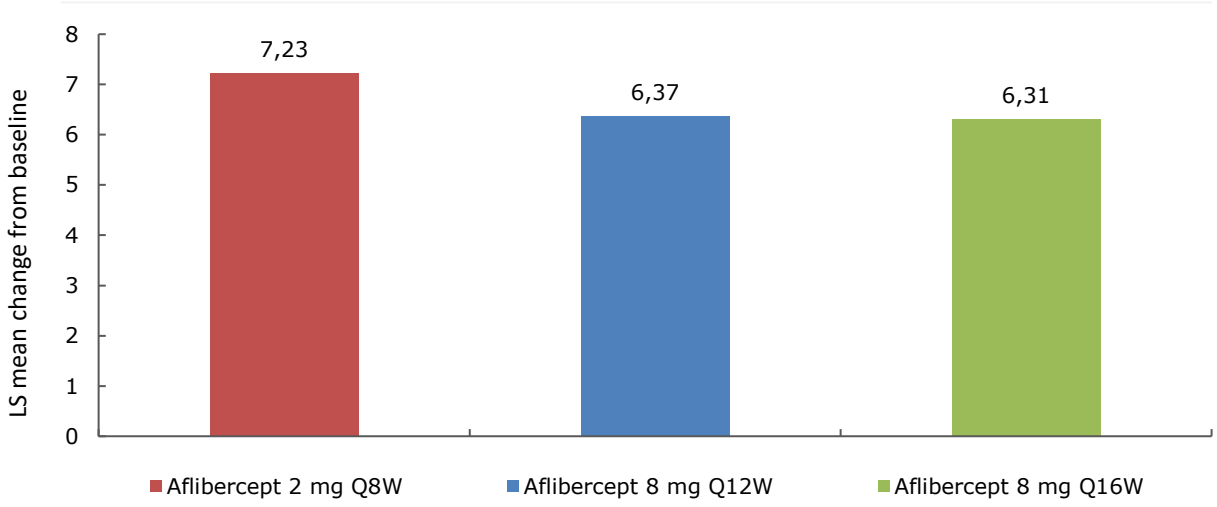
The key secondary endpoint (mean change in BCVA at week 60) demonstrated that non-inferiority on the primary endpoint (mean change in BCVA at week 48) between aflibercept 8 mg administered in two extended dosing regimens (Q12W and Q16W) and aflibercept 2 mg Q8W was maintained at week 60.

Mean change in best corrected visual acuity as measured by Early Treatment Diabetic Retinopathy Study letter score for aflibercept 8 mg (Q12W and Q16W) were non-inferior to aflibercept 2 mg at week 60

In the PULSAR study, non-inferiority to aflibercept 2 mg Q8W in terms of LS mean improvement from BCVA as measured by ETDRS letter score at week 60 was maintained at week 60 for both aflibercept 8 mg dosing schedules (p=0.0002 for Q12W and p<0.0001 for Q16W, respectively; (Figure 6 and Table 9).

The results for the key secondary endpoint in the FAS population are supported by the corresponding results for the PPS population and all subgroup and sensitivity analyses; for more details, see PULSAR Clinical Study Report (week 60).

Figure 6 Least squares mean change in BCVA as measured by ETDRS letter score at week 60



Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

Source: PULSAR Clinical Study Report (week 60).

Table 9 Change from baseline in BCVA measured by the ETDRS letter score at week 60

According to EP-SAP	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	 Q16W n=338
Number of patients with week 60 data	268	283	282
Baseline mean	58.9	59.9	60.0
Arithmetic mean (SD) change from baseline	7.8 (12.6)	6.6 (13.6)	6.6 (11.7)
LS mean (SE) change from baseline	7.23 (0.68)	6.37 (0.74)	6.31 (0.66)
p value of 1-sided test for non-inferiority at a margin of 4 letters	-	0.0002	<0.0001
Difference in LS mean versus aflibercept 2 mg Q8W (95% CI)	-	-0.86 (-2.57 to 0.84)	-0.92 (-2.51 to 0.66)

BCVA= best-corrected visual acuity (best possible vision an eye can see with spectacles or other visual corrective devices assessed using ETDRS chart); CI=confidence interval; EP-SAP=European Medicines Agency/Pharmaceuticals and Medical Devices Agency statistical analysis plan; ETDRS=Early Treatment Diabetic Retinopathy Study; LS=least squares; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; SD=standard deviation; SE=standard error.

Source: PULSAR Clinical Study Report (week 60).

Proportion of patients losing ≥15 letters at week 60 were comparable between 8 mg dosing groups and the group treated with aflibercept 2 mg

The proportion of participants who lost ≥15 letters in BCVA from baseline at week 60 was <7% in all 3 treatment groups, with only small numerical differences between the groups (Table 10).

Table 10 Proportion of participants losing ≥15 letters in BCVA from baseline at week 60

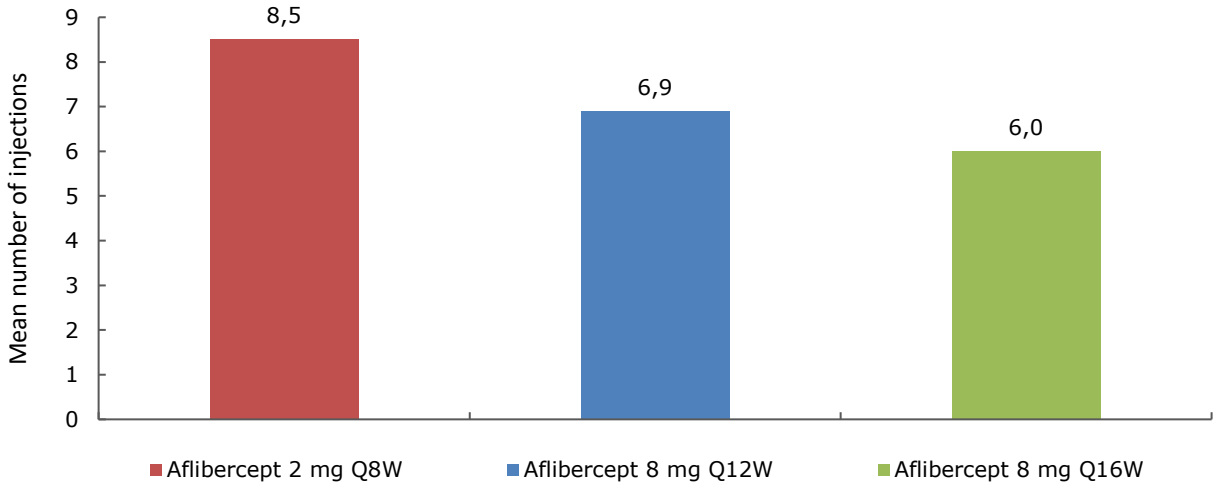
Exploratory endpoints through week 60, full analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg *(p value versus aflibercept 2 mg Q8W)*	
		Q12W n=335	Q16W n=338
Proportion of participants	N=335	N=334	N=337
▪ Gained ≥ 15 letters in BCVA	23.3%	23.7% *(NR)*	23.1% *(NR)*
▪ Gained ≥ 10 letters in BCVA	42.7%	41.0% *(NR)*	37.4% *(NR)*
▪ Gained ≥ 5 letters in BCVA	64.5%	57.2% *(NR)*	60.5% *(NR)*
▪ Lost ≥ 15 letters in BCVA	4.2%	6.6% *(NR)*	5.0% *(NR)*
▪ Lost ≥ 10 letters in BCVA	7.8%	9.0% *(NR)*	8.9% *(NR)*
▪ Lost ≥ 5 letters in BCVA	10.4%	13.5% *(NR)*	14.8% *(NR)*

Source: PULSAR Clinical Study Report (week 60).

Mean number of injections at week 60 were numerical lower for patients treated with aflibercept 8 mg

Over the 48-week period, patients treated with aflibercept 8 mg received fewer injections compared with aflibercept 2 mg. The mean number of injections over 48 weeks was 6.9 in the aflibercept 8 mg Q12W group, 6.0 in the aflibercept 8 mg Q16W group, and 8.5 in the aflibercept 2 mg Q8W group (Figure 7).

Figure 7 Mean number of aflibercept injections through week 60



Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

Source: PULSAR Clinical Study Report (week 60).

Aflibercept 8 mg demonstrated longer duration as a high number of patients were maintained on the initial assigned dosing interval or extended to a longer dosing interval

Maintenance of dosing interval with aflibercept 8 mg after 3 loading doses

Proportion of participants maintained with Q16W treatment interval through week 60 in Q16W group

The majority of patients from aflibercept 8 mg Q16W group (74.1%) were maintained on assigned dosing interval through week 60 (Table 11).

Proportion of participants maintained with Q12W or longer interval through week 60 in the Q12W and Q1W6 groups

The majority of patients from aflibercept 8 mg Q12W group (77.8%) and Q16W group (85.4%) were maintained on Q12W or a longer dosing intervals through week 60. In the pooled aflibercept 8 mg groups, a substantial majority (81.6%) of patients maintained a Q12W or longer dosing interval through week 60 (Table 11).

Proportion of participants maintained with Q12W or Q16W or Q20W treatment interval as the last treatment interval at week 60, in the Q12W and Q16W groups, respectively

The proportion of participants with Q12W or longer as the last treatment interval at week 60 was 84.6% in the aflibercept 8 mg Q12W group and 90.0% in the Q16W group, and 87.3% in the pooled aflibercept 8 mg groups. The proportion of participants with Q16W or Q20W as the last treatment interval at week 60 was 77.3% in the aflibercept 8 mg Q16W group, whereas 38.5% of the participants in the aflibercept 8 mg Q16W group were assigned to Q20W treatment interval as the last treatment interval (Table 11).

Table 11 Exposure to study treatment through week 60: Dosing intervals

n (%)	Aflibercept 8 mg		
	Q12W n=335	Q16W n=338	Pooled n=628
Patients with maintained Q12W or longer dosing interval	242 (77.8%)	264 (85.4%)	506 (81.6%)
Patients with maintained Q16W dosing interval	-	229 (74.1%)	-
Patients with Q12W or longer as the last intended dosing interval	263 (84.6%)	278 (90.0%)	541 (87.3%)
Patients with Q16W or longer as the last intended dosing interval	134 (43.1%)	239 (77.3%)	373 (60.2%)
Patients with Q20W as the last intended dosing interval	-	119 (38.5%)	-
Patients shortened anytime	69 (22.2%)	80 (25.9%)	149 (24.0%)

Patients shortened to Q8W dosing interval anytime	69 (22.2%)	45 (14.6%)	114 (18.4%)
Patients shortened to Q12W dosing interval anytime (without shortening to Q8W)		35 (11.3%)	
Subjects extended dosing interval anytime	152 (48.9%)	135 (43.7%)	287 (46.3%)

Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; Q20W=every 20 weeks.

Source: PULSAR Clinical Study Report (week 60).

Clinical efficacy from PULSAR study: Week 96 results

Mean change in best corrected visual acuity as measured by Early Treatment Diabetic Retinopathy Study letter score for aflibercept 8 mg (Q12W and Q16W) were non-inferior to aflibercept 2 mg at week 96

Both arithmetic mean changes and LS mean changes from baseline in BCVA measured by the ETDRS letter score by visit were similar across aflibercept 2 mg Q8W, aflibercept 8 mg Q12W, and aflibercept 8 mg Q16W treatment groups, with minor numerical differences but not considered clinically relevant, demonstrating robustness of results through week 96 (Table 12)

Table 12 Mean change in best corrected visual acuity as measured by Early Treatment Diabetic Retinopathy Study ETDRS letter score at week 96

Treatment	LS mean (SE) chg from BL	Arith mean (SD) chg from BL (a)	Baseline mean(s)	Number of subjects with Week 96 data	DF	Contrast(b)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(c)
Q12W (N=335)	5.59(0.77)	5.9(14.2)	59.9	256	1006.4	Q12W-Q8W	3.25	0.0006	0.8635	-1.01 (-2.82,0.80)
Q16W (N=338)	5.52 (0.75)	5.6(13.7)	60.0	264	989.0	Q16W-Q8W	3.21	0.0007	0.8823	-1.08 (-2.87,0.71)
Q8W (N=336)	6.60 (0.73)	7.4 (13.8)	58.9	243						

Proportion of patients losing ≥15 letters at week 96 were comparable between 8 mg dosing groups and the group treated with aflibercept 2 mg

The proportion of participants who lost ≥15 letters in BCVA from baseline at week 96 was <8% in all 3 treatment groups, with only small numerical differences between the groups (Table 13).

Table 13 Proportion of patients losing letters in BCVA at week 96

Exploratory endpoints through week 96, full analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg *(%)*	
		Q12W n=335	Q16W n=338
Proportion of participants	N=336	N=335	N=338
▪ Lost ≥ 15 letters in BCVA	17/335 (5.1%)	26/334 (7.8%)	26/337 (7.7%)
▪ Lost ≥ 10 letters in BCVA	25/335 (7.5%)	34/334 (10.2%)	42/337 (12.5%)
▪ Lost ≥ 5 letters in BCVA	52/335 (15.5%)	50/334 (15.0%)	59/337 (17.5%)

Mean number of injections at week 96 were numerical lower for patients treated with aflibercept 8 mg

Over the 96-week period, patients treated with aflibercept 8 mg received fewer injections compared with aflibercept 2 mg. The mean number of injections in the 2nd year of treatment was 3.7 in the aflibercept 8 mg Q12W group, 3.0 in the aflibercept 8 mg Q16W group, and 5.8 in the aflibercept 2 mg Q8W group (Table 14 and Figure 7).

Table 14 Mean number of injections through week 96

	Q8W	Q12W	Q16W	All HD
	N=286	N=291	N=292	N=583
Total number of active injections in 2nd year, n	1671	1064	887	1951
Number of active injections in 2nd year. n (%)				
0	1 (0.3%)	0	0	0
1	0	0	1 (0.3%)	1 (0.2%)
2	0	8 (2.7%)	109 (37.3%)	117 (20.1%)
3	2 (0.7%)	159 (54.6%)	117 (40.1%)	276 (47.3%)
4	3 (1.0%)	76 (26.1%)	30 (10.3%)	106 (18.2%)
5	27 (9.4%)	22 (7.6%)	13 (4.5%)	35 (6.0%)

6	253 (88.5%)	25 (8.6%)	22 (7.5%)	47 (8.1%)
7	0	1 (0.3%)	0	1 (0.2%)
Number of active injections in 2nd year				
n	286	291	292	583
Mean (SD)	5.8 (0.5)	3.7 (1.0)	3.0 (1.2)	3.3 (1.1)
Median	6.0	3.0	3.0	3.0
Q1, Q3	6.0, 6.0	3.0, 4.0	2.0, 3.0	3.0, 4.0
Min, Max	0, 6	2, 7	1, 6	1, 7

Aflibercept 8 mg demonstrated longer duration as a high number of patients were maintained on the initial assigned dosing interval or extended to a longer dosing interval

Maintenance and extension of dosing intervals at week 96 with aflibercept 8 mg after 3 loading doses

Table 15 Maintenance of dosing interval with aflibercept 8 mg at week 96

	Q8W N=286	Q12W N=291	Q16W N=292	All HD N=583
Subjects maintained with q12 or longer dosing interval (a), n (%)		219 (75.3%)	238 (81.5%)	457 (78.4%)
Subjects maintained with q16 or longer dosing interval (b), n (%)			205 (70.2%)	
Subjects maintained and extended to q20 or longer dosing interval (c), n (%)		110 (37.8%)	142 (48.6%)	252 (43.2%)
Subjects maintained and extended to q24 dosing interval (d), n (%)		72 (24.7%)	87 (29.8%)	159 (27.3%)
Subjects with q12 or longer dosing interval as the last intended dosing interval (e), n (%)		252 (86.6%)	260 (89.0%)	512 (87.8%)
Subjects with q16 or longer dosing interval as the last intended dosing interval (e), n (%)		185 (63.6%)	229 (78.4%)	414 (71.0%)
Subjects with q20 or longer dosing interval as the last intended dosing interval (e), n (%)		118 (40.5%)	155 (53.1%)	273 (46.8%)
Subjects with q24 dosing interval as the last intended dosing interval (e), n (%)		72 (24.7%)	90 (30.8%)	162 (27.8%)

Table 16 Extension of dosing intervals with aflibercept 8 mg at week 96

	Q12W N=291	Q16W N=292	All HD N=583
Subjects extended dosing interval anytime, n (%)	214 (73.5%)	187 (64.0%)	401 (68.8%)
Of these,			
Q12W subjects extended to q16 dosing interval at Week 56, n (%)	127 (43.6%)		
Shortened back to q12 at Week 72 (i.e., one q16 interval), n (%)	1 (0.3%)		
Maintained at q16 Week 72 (i.e., two q16 interval), n (%)	28 (9.6%)		
Extended to q20 at week 72 (ie. one q16 plus one q20), n (%)	90 (30.9%)		
Shortened back to q16 at Week 92 (i.e. one q20 interval), n (%)	1 (0.3%)		
Maintained at q20 at Week 92 (i.e., one q20, plus one incomplete q20), n (%)	13 (4.5%)		
Extended to q24 at Week 92 (i.e., one q20, plus one incomplete q24), n (%)	72 (24.7%)		
Q16W subjects extended to q20 dosing interval at Week 56, n (%)		111 (38.0%)	
Shortened back to q16 at Week 76 (i.e., one q20 interval), n (%)		2 (0.7%)	
Maintained at q20 at Week 76 (i.e., two q20 intervals), n (%)		31 (10.6%)	
Extended to q24 at Week 76 (i.e., one q20, plus one incomplete q24), n (%)		76 (26.0%)	

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

PULSAR study: Week 48 safety results for aflibercept 8 mg were similar to aflibercept 2 mg

Proportion of participants with any ocular treatment-emergent adverse events and any non-ocular treatment-emergent adverse events through week 48

The proportions of patients who experienced any TEAEs were similar across all 3 treatment groups, with 75.1% in the aflibercept 8 mg Q16W group and 72.2% in the aflibercept 8 mg Q12W group (73.7% in the pooled Q12W and Q16W treatment groups) versus 71.4% in the aflibercept 2 mg Q8W group (Table 17). The proportions of patients with any ocular TEAEs through week 48 were similar (Table 17) across all 3 treatment groups (47.5% in the aflibercept 8 mg Q12W group, 46.4% in the aflibercept 8 mg Q16W group, and 47.0% in the pooled Q12W and Q16W treatment groups versus 47.6% in the aflibercept 2 mg Q8W group).

The proportions of patients with any ocular TEAEs in the study eye were also similar across all 3 treatment groups (38.5% in the aflibercept 8 mg Q12W group, 37.6% in the aflibercept 8 mg Q16W group, and 38.0% in the pooled Q12W and Q16W treatment groups versus 38.7% in the aflibercept 2 mg Q8W group). 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 study eye of mild, moderate, and severe intensity were 26.2%, 11.0%, and 0.9%, respectively. In the aflibercept 2 mg Q8W group, the proportions were 31.3%, 6.8%, and 0.6%, respectively (Table 17).

The proportions of patients with TEAEs related to intraocular inflammation in the study eye were low and similar across the treatment groups. Furthermore, there were no clinically relevant differences in proportions of patients with increased intraocular pressure between treatment groups which was present in 3.0% of patients in the pooled aflibercept 8 mg Q12W and Q16W treatment groups, and 2.1% of patients in the aflibercept 2 mg Q8W group (Table 17).

Proportion of participants with any study-drug-related ocular treatment-emergent adverse events and any non-ocular treatment-emergent adverse events through week 48

The proportions of patients who experienced any study-drug-related TEAEs were similar across all 3 treatment groups and generally of low frequency, with 3.8% in the aflibercept 8 mg Q16W group and 6.6% in the aflibercept 8 mg Q12W group (5.2% in the pooled Q12W and Q16W treatment groups) versus 3.9% in the aflibercept 2 mg Q8W group (Table 17). Any study-drug-related ocular TEAEs were reported in 3.3% of participants in the aflibercept 8 mg Q16W group and 6.0% of participants in the aflibercept 8 mg Q12W group (4.6% in the pooled Q12W and Q16W treatment groups) compared with 3.0% of participants in the aflibercept 2 mg Q8W group (Table 17).

Ocular TEAEs in the study eye judged to be related to study drug were generally of low frequency and mostly reported for single participants only. Ocular TEAEs in the study eye judged to be related to study drug were reported in 4.6% of participants in the pooled aflibercept 8 mg groups and in 2.7% of participants in the aflibercept 2 mg Q8W group. The only ocular TEAEs in the study eye judged to be related to study drug that were reported for with a frequency of >1% in any treatment group was visual acuity reduced (Table 17).

Proportion of participants with any ocular treatment-emergent adverse events and any non-ocular treatment-emergent adverse events leading to discontinuation of the study drug through week 48

The proportions of patients who experienced any TEAEs leading to discontinuation of a study drug were the same across all groups and generally of low frequency with 1.5% in the aflibercept 8 mg Q16W group, 1.5% in the aflibercept 8 mg Q12W group (1.5% in the pooled Q12W and Q16W treatment groups) versus 1.5% in the aflibercept 2 mg Q8W group. The proportions of patients who experienced any ocular TEAEs leading to discontinuation of study drug were 0.9% in the aflibercept 8 mg Q16W group, in the aflibercept 8 mg Q12W group and in the pooled Q12W and Q16W treatment groups versus 0.3% in the aflibercept 2 mg Q8W group (Table 17).

Ocular TEAEs in the study eye that resulted in discontinuation of the study drug affected few participants (Table 17): 0.9% of patients in the pooled aflibercept 8 mg Q12W and Q16W treatment groups and 0.3% participants in the aflibercept 2 mg Q8W group. Similarly, non-ocular TEAEs resulted in discontinuation of the study drug in 0.6% participants in the pooled aflibercept 8 mg Q12W and Q16W treatment groups and 1.2% participants in the aflibercept 2 mg Q8W group (Table 17).

Proportion of participants with treatment-emergent adverse events related to intravitreal injection procedure in the study eye through week 48

The proportions of ocular TEAEs related to intravitreal injection procedure in the study eye were similar between aflibercept 8 mg groups and aflibercept 2 mg group. Intravitreal injection procedure-related TEAEs in the study eye were reported in 9.5% of the participants in the pooled aflibercept 8 mg groups and in 10.4% of participants in the aflibercept 2 mg Q8W group (Table 17). The most common ocular TEAEs related to intravitreal injection procedure in the study eye, reported in ≥5 participants, were increased intraocular pressure, conjunctival haemorrhage, vitreous floaters, ocular hypertension, and sensation of foreign body.

Proportion of participants with any ocular severe adverse events and any non-ocular serious adverse events through week 48

The proportion of participants with ocular treatment-emergent serious adverse events (TESAEs) in the study eye was low in all treatment groups and numerically higher in the aflibercept 8 mg Q12W and aflibercept 8 mg Q16W groups. These TESAEs were reported in 1.8% participants from the aflibercept 8 mg Q12W group and in 1.5% participants from the aflibercept 8 mg Q16W group (1.6% in the pooled Q12W and Q16W treatment groups) versus 0.6% participants from the aflibercept 2 mg Q8W group. Most of these ocular TESAEs in the study eye were infrequent and reported in single participants in any treatment group; the exceptions were retinal detachment (reported in 3 participants in the aflibercept 8 mg Q12W group and 1 participant in the aflibercept 8 mg Q16W group) and intraocular pressure increased (reported in 2 participants in the aflibercept 8 mg Q12W group and none in the aflibercept 8 mg Q16W group). Retinal detachment and intraocular pressure increased were not reported in any participants from the aflibercept 2 mg Q8W group.

Non-ocular TESAEs were reported in 9.5% participants in the aflibercept 8 mg Q16W group and 10.1% in the aflibercept 8 mg Q12W group (9.8% in the pooled Q12W and Q16W treatment groups) versus 13.7% in the aflibercept 2 mg Q8W group (Table 18).

Table 17: Overall summary of all adverse events through week 48

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Aflibercept 8 mg Q16W n=338	Pooled n=673
Any AE	240 (71.4%)	242 (72.2%)	254 (75.1%)	496 (73.7%)
Any pre-treatment AE	33 (9.8%)	15 (4.5%)	34 (10.1%)	49 (7.3%)
Any TEAE	235 (69.9%)	239 (71.3%)	249 (73.7%)	488 (72.5%)
Any post-treatment AE	2 (0.6%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Any ocular TEAE	160 (47.6%)	159 (47.5%)	157 (46.4%)	316 (47.0%)
Any ocular TEAE in study eye	130 (38.7%)	129 (38.5%)	127 (37.6%)	256 (38.0%)
Eye disorders	110 (32.7%)	114 (34.0%)	111 (32.8%)	225 (33.4%)
Visual acuity reduced	20 (6.0%)	12 (3.6%)	18 (5.3%)	30 (4.5%)
Cataract	10 (3.0%)	12 (3.6%)	12 (3.6%)	24 (3.6%)
Retinal haemorrhage	14 (4.2%)	11 (3.3%)	10 (3.0%)	21 (3.1%)
Vitreous floaters	11 (3.3%)	4 (1.2%)	12 (3.6%)	16 (2.4%)
Subretinal fluid	11 (3.3%)	10 (3.0%)	5 (1.5%)	15 (2.2%)
Vitreous detachment	5 (1.5%)	6 (1.8%)	9 (2.7%)	15 (2.2%)
Neovascular age-related macular degeneration	2 (0.6%)	7 (2.1%)	7 (2.1%)	14 (2.1%)
Conjunctival haemorrhage	5 (1.5%)	8 (2.4%)	5 (1.5%)	13 (1.9%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Aflibercept 8 mg Q16W n=338	Aflibercept 8 mg Pooled n=673
Macular thickening	3 (0.9%)	7 (2.1%)	6 (1.8%)	13 (1.9%)
Dry eye	4 (1.2%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Eye pain	2 (0.6%)	5 (1.5%)	4 (1.2%)	9 (1.3%)
Retinal pigment epithelial tear	3 (0.9%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Age-related macular degeneration	1 (0.3%)	5 (1.5%)	3 (0.9%)	8 (1.2%)
Macular oedema	8 (2.4%)	1 (0.3%)	7 (2.1%)	8 (1.2%)
Macular fibrosis	4 (1.2%)	3 (0.9%)	3 (0.9%)	6 (0.9%)
Ocular hypertension	1 (0.3%)	2 (0.6%)	4 (1.2%)	6 (0.9%)
Eye irritation	0	1 (0.3%)	4 (1.2%)	5 (0.7%)
Punctate keratitis	4 (1.2%)	1 (0.3%)	4 (1.2%)	5 (0.7%)
Retinal oedema	2 (0.6%)	1 (0.3%)	4 (1.2%)	5 (0.7%)
Retinal pigment epitheliopathy	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Dry age-related macular degeneration	4 (1.2%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Detachment of macular retinal pigment epithelium	4 (1.2%)	0	1 (0.3%)	1 (0.1%)
Investigations	7 (2.1%)	14 (4.2%)	12 (3.6%)	26 (3.9%)
Intraocular pressure increased	7 (2.1%)	11 (3.3%)	9 (2.7%)	20 (3.0%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Aflibercept 8 mg Q16W n=338	Pooled n=673
General disorders and administration site conditions	12 (3.6%)	9 (2.7%)	9 (2.7%)	18 (2.7%)
Sensation of foreign body	7 (2.1%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
Infections and infestations	5 (1.5%)	9 (2.7%)	3 (0.9%)	12 (1.8%)
Conjunctivitis	4 (1.2%)	5 (1.5%)	3 (0.9%)	8 (1.2%)
Injury, poisoning and procedural complications	6 (1.8%)	6 (1.8%)	4 (1.2%)	10 (1.5%)
Corneal abrasion	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Any ocular TEAE in fellow eye	89 (26.5%)	80 (23.9%)	84 (24.9%)	164 (24.4%)
Any non-ocular TEAE	178 (53.0%)	175 (52.2%)	182 (53.8%)	357 (53.0%)
Any study-drug-related TEAE	13 (3.9%)	22 (6.6%)	13 (3.8%)	35 (5.2%)
Any study-drug-related ocular TEAE	10 (3.0%)	20 (6.0%)	11 (3.3%)	31 (4.6%)
Any study-drug-related ocular TEAE in study eye	9 (2.7%)	20 (6.0%)	11 (3.3%)	31 (4.6%)
Visual acuity reduced	0	4 (1.2%)	1 (0.3%)	5 (0.7%)
Any study-drug-related ocular TEAE in fellow eye	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Any study-drug-related non-ocular TEAE	3 (0.9%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Any TEAE related to intravitreal injection procedure	37 (11.0%)	38 (11.3%)	33 (9.8%)	71 (10.5%)
Any ocular TEAE related to intravitreal injection procedure	37 (11.0%)	37 (11.0%)	33 (9.8%)	70 (10.4%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Aflibercept 8 mg Q16W n=338	Aflibercept 8 mg Pooled n=673
Any ocular TEAE related to intravitreal injection procedure in study eye	35 (10.4%)	32 (9.6%)	32 (9.5%)	64 (9.5%)
Intraocular pressure increased	4 (1.2%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Conjunctival haemorrhage	3 (0.9%)	6 (1.8%)	2 (0.6%)	8 (1.2%)
Vitreous floaters	7 (2.1%)	1 (0.3%)	5 (1.5%)	6 (0.9%)
Ocular hypertension	1 (0.3%)	2 (0.6%)	3 (0.9%)	5 (0.7%)
Sensation of foreign body	6 (1.8%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Any ocular TEAE related to intravitreal injection procedure in fellow eye	5 (1.5%)	5 (1.5%)	4 (1.2%)	9 (1.3%)
Any non-ocular TEAE related to intravitreal injection procedure	0	4 (1.2%)	1 (0.3%)	5 (0.7%)
Any TEAE related to protocol-required procedure	19 (5.7%)	13 (3.9%)	15 (4.4%)	28 (4.2%)
Any ocular TEAE related to protocol-required procedure	12 (3.6%)	8 (2.4%)	9 (2.7%)	17 (2.5%)
Any ocular TEAE related to protocol-required procedure in study eye	11 (3.3%)	7 (2.1%)	9 (2.7%)	16 (2.4%)
Any ocular TEAE related to protocol-required procedure in fellow eye	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Any non-ocular TEAE related to protocol-required procedure	7 (2.1%)	6 (1.8%)	6 (1.8%)	12 (1.8%)
Any TEAE related to fellow eye treatment	59 (17.6%)	52 (15.5%)	64 (18.9%)	116 (17.2%)
Any ocular TEAE related to fellow eye treatment	51 (15.2%)	40 (11.9%)	47 (13.9%)	87 (12.9%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Aflibercept 8 mg Q16W n=338	Pooled n=673
Any ocular TEAE related to fellow eye treatment in study eye	34 (10.1%)	22 (6.6%)	27 (8.0%)	49 (7.3%)
Any ocular TEAE related to fellow eye treatment in fellow eye	41 (12.2%)	35 (10.4%)	39 (11.5%)	74 (11.0%)
Any non-ocular TEAE related to fellow eye treatment	41 (12.2%)	36 (10.7%)	44 (13.0%)	80 (11.9%)
Any TEAE leading to discontinuation of study druga	5 (1.5%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Any ocular TEAE leading to discontinuation of study drug	1 (0.3%)	3 (0.9%)	3 (0.9%)	6 (0.9%)
Any ocular TEAE leading to discontinuation of study drug in study eye	1 (0.3%)	3 (0.9%)	3 (0.9%)	6 (0.9%)
Any ocular TEAE leading to discontinuation of study drug in fellow eye	0	0	0	0
Any non-ocular TEAE leading to discontinuation of study drug	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Any serious AE	51 (15.2%)	43 (12.8%)	39 (11.5%)	82 (12.2%)
Any serious pre-treatment AE	0	0	1 (0.3%)	1 (0.1%)
Any serious TEAE	49 (14.6%)	41 (12.2%)	37 (10.9%)	78 (11.6%)
Any serious post-treatment AE	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Any ocular serious TEAE	3 (0.9%)	7 (2.1%)	5 (1.5%)	12 (1.8%)
Any ocular serious TEAE in study eye	2 (0.6%)	6 (1.8%)	5 (1.5%)	11 (1.6%)
Any ocular serious TEAE in fellow eye	2 (0.6%)	1 (0.3%)	0	1 (0.1%)
Any non-ocular serious TEAE	46 (13.7%)	34 (10.1%)	32 (9.5%)	66 (9.8%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Q16W n=338	Pooled n=673
Any study-drug-related serious TEAE	2 (0.6%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Any study-drug-related ocular serious TEAE	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Any study-drug-related ocular serious TEAE in study eye	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Any study-drug-related ocular serious TEAE in fellow eye	0	0	0	0
Any study drug related non-ocular serious TEAE	2 (0.6%)	0	2 (0.6%)	2 (0.3%)
Any serious TEAE related to intravitreal injection procedure	0	3 (0.9%)	2 (0.6%)	5 (0.7%)
Any ocular serious TEAE related to intravitreal injection procedure	0	2 (0.6%)	2 (0.6%)	4 (0.6%)
Any ocular serious TEAE related to intravitreal injection procedure in study eye	0	2 (0.6%)	2 (0.6%)	4 (0.6%)
Any ocular serious TEAE related to intravitreal injection procedure in fellow eye	0	0	0	0
Any non-ocular serious TEAE related to intravitreal injection procedure	0	1 (0.3%)	0	1 (0.1%)
Any serious TEAE related to protocol-required procedure	0	1 (0.3%)	0	1 (0.1%)
Any ocular serious TEAE related to protocol-required procedure	0	0	0	0
Any ocular serious TEAE related to protocol-required procedure in study eye	0	0	0	0

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Aflibercept 8 mg Q16W n=338	Aflibercept 8 mg Pooled n=673
Any ocular serious TEAE related to protocol-required procedure in fellow eye	0	0	0	0
Any non-ocular serious TEAE related to protocol-required procedure	0	1 (0.3%)	0	1 (0.1%)
Any serious TEAE related to fellow eye treatment	12 (3.6%)	9 (2.7%)	9 (2.7%)	18 (2.7%)
Any ocular serious TEAE related to fellow eye treatment	1 (0.3%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Any ocular serious TEAE related to fellow eye treatment in study eye	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
Any ocular serious TEAE related to fellow eye treatment in fellow eye	0	1 (0.3%)	0	1 (0.1%)
Any non-ocular serious TEAE related to fellow eye treatment	11 (3.3%)	6 (1.8%)	8 (2.4%)	14 (2.1%)
Any AE with outcome death	5 (1.5%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Any pre-treatment AE with outcome death	0	0	0	0
Any TEAE with outcome death	5 (1.5%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Any post-treatment AE with outcome death	0	0	0	0
Any TEAE of intraocular inflammation in the study eye	2 (0.6%)	4 (1.2%)	1 (0.3%)	5 (0.7%)
Any adjudicated treatment-emergent APTC events[b]	5 (1.5%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Any TEAE of hypertension	12 (3.6%)	16 (4.8%)	16 (4.7%)	32 (4.8%)
Any TEAE of nasal mucosal finding	0	0	2 (0.6%)	2 (0.3%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Aflibercept 8 mg Q16W n=338	Pooled n=673
Maximum intensity (% per treatment group)				
Missing intensity for any ocular TEAE in study eye	0	0	0	0
Mild intensity for any ocular TEAE in study eye	105 (31.3%)	86 (25.7%)	90 (26.6%)	176 (26.2%)
Moderate intensity for any ocular TEAE in study eye	23 (6.8%)	39 (11.6%)	35 (10.4%)	74 (11.0%)
Severe intensity for any ocular TEAE in study eye	2 (0.6%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
Missing intensity for any ocular TEAE in fellow eye	0	0	0	0
Mild intensity for any ocular TEAE in fellow eye	69 (20.5%)	55 (16.4%)	58 (17.2%)	113 (16.8%)
Moderate intensity for any ocular TEAE in fellow eye	19 (5.7%)	23 (6.9%)	25 (7.4%)	48 (7.1%)
Severe intensity for any ocular TEAE in fellow eye	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
Missing intensity for any non-ocular TEAE	0	0	0	0
Mild intensity for any non-ocular TEAE	89 (26.5%)	103 (30.7%)	97 (28.7%)	200 (29.7%)
Moderate intensity for any non-ocular TEAE	61 (18.2%)	55 (16.4%)	73 (21.6%)	128 (19.0%)
Severe intensity for any non-ocular TEAE	28 (8.3%)	17 (5.1%)	12 (3.6%)	29 (4.3%)
Missing intensity for any ocular serious TEAE in study eye	0	0	0	0
Mild intensity for any ocular serious TEAE in study eye	1 (0.3%)	0	0	0
Moderate intensity for any ocular serious TEAE in study eye	0	3 (0.9%)	4 (1.2%)	7 (1.0%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Aflibercept 8 mg Q16W n=338	Aflibercept 8 mg Pooled n=673
Severe intensity for any ocular serious TEAE in study eye	1 (0.3%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Missing intensity for any ocular serious TEAE in fellow eye	0	0	0	0
Mild intensity for any ocular serious TEAE in fellow eye	1 (0.3%)	0	0	0
Moderate intensity for any ocular serious TEAE in fellow eye	1 (0.3%)	1 (0.3%)	0	1 (0.1%)
Severe intensity for any ocular serious TEAE in fellow eye	0	0	0	0
Missing intensity for any non-ocular TEAE	0	0	0	0
Mild intensity for any non-ocular TEAE	5 (1.5%)	7 (2.1%)	1 (0.3%)	8 (1.2%)
Moderate intensity for any non-ocular TEAE	16 (4.8%)	10 (3.0%)	20 (5.9%)	30 (4.5%)
Severe intensity for any non-ocular TEAE	25 (7.4%)	17 (5.1%)	11 (3.3%)	28 (4.2%)

AE=adverse event; APTC=Anti-Platelet Trialists' Collaboration; CV=cardiovascular; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; 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.

Post-treatment AEs are defined as AEs that started >30 days after the last injection (active or sham) in the study.

Fellow eye treatment is defined as commercial aflibercept (2 mg), which was not provided by the sponsor through study medication supplies.

[a]There were 9 participants who reported ≥1 TEAE resulting in discontinuation of study drug, but the reason for premature discontinuation of treatment was not recorded as an adverse event. In addition, there were 2 participants for whom the primary reason for premature discontinuation of treatment was recorded as an adverse event, but no corresponding TEAEs resulting in discontinuation of study drug were reported.

[b]There was 1 more participant in the Q16W group with an APTC event of CV death. Because of a change in the AE term (from death to unspecified fatal event) in the latest coding transfer, this was missed for marking as APTC event in the clinical database and is, therefore, not displayed in this summary table for treatment emergent APTC events.

Source: PULSAR Clinical Study Report (week 48).

Table 18: Ocular and non-ocular TESAEs, safety analysis set week 48

Primary system organ class Preferred term MedDRA version 25.0	Aflibercept 2 mg	Aflibercept 8 mg		
	Q8W n=336	Q12W n=335	Q16W n=338	Pooled n=673
Ocular TESAEs in study eye				
Number (%) of subjects with ≥1 such AE	2 (0.6%)	6 (1.8%)	5 (1.5%)	11 (1.6%)
Eye disorders	2 (0.6%)	4 (1.2%)	4 (1.2%)	8 (1.2%)
Retinal detachment	0	3 (0.9%)	1 (0.3%)	4 (0.6%)
Retinal haemorrhage	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Angle closure glaucoma	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Cataract	0	1 (0.3%)	0	1 (0.1%)
Choroidal detachment	0	1 (0.3%)	0	1 (0.1%)
Vitreous haemorrhage	0	0	1 (0.3%)	1 (0.1%)
Investigations	0	2 (0.6%)	0	2 (0.3%)
Intraocular pressure increased	0	2 (0.6%)	0	2 (0.3%)
Injury, poisoning and procedural complications	0	0	1 (0.3%)	1 (0.1%)
Skin laceration	0	0	1 (0.3%)	1 (0.1%)
Non-ocular TESAEs occurring in >1 participant				
Number (%) of subjects with ≥1 such AE	46 (13.7%)	34 (10.1%)	32 (9.5%)	66 (9.8%)
Pneumonia	1 (0.3%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Cellulitis	0	2 (0.6%)	0	2 (0.3%)
Pyelonephritis acute	0	0	2 (0.6%)	2 (0.3%)

Urinary tract infection	4 (1.2%)	1 (0.3%)	0	1 (0.1%)
Bladder neoplasm	3 (0.9%)	0	0	0
Angina pectoris	0	0	3 (0.9%)	3 (0.4%)
Osteoarthritis	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Back pain	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Syncope	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cerebrovascular accident	2 (0.6%)	1 (0.3%)	0	1 (0.1%)
Chronic obstructive pulmonary disease	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Chest pain	0	2 (0.6%)	0	2 (0.3%)
Upper limb fracture	2 (0.6%)	0	0	0
Hyponatraemia	2 (0.6%)	0	2 (0.6%)	2 (0.3%)

AE=adverse event; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; TESAE=treatment-emergent serious 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.
Only the most severe intensity is counted for multiple occurrences of the same TEAE in 1 individual.
Missing is considered to be the lowest category of intensity.
System organ classes and preferred terms are sorted by decreasing order of frequency in the pooled Aflibercept 8 mg groups.

Source: PULSAR Clinical Study Report (week 48).

PULSAR study – 60-week safety results for aflibercept 8 mg were similar to aflibercept 2 mg

Proportion of participants with any ocular treatment-emergent adverse events and any non-ocular treatment-emergent adverse events through week 60

The proportions of patients who experienced any TEAEs were similar across all 3 treatment groups, occurring in 82.2% of the aflibercept 8 mg Q16W group and 77.0% of the aflibercept 8 mg Q12W group (79.6% in the pooled Q12W and Q16W treatment groups) versus 78.3% of the aflibercept 2 mg Q8W group (Table 19). The proportions of patients with any ocular TEAEs through week 60 were similar (Table 19) across all 3 treatment groups: 51.0% in the aflibercept 8 mg Q12W group, 53.3% in the aflibercept 8 mg Q16W group, and 52.2% in the pooled Q12W and Q16W treatment groups versus 53.9% in the aflibercept 2 mg Q8W group.

The proportions of patients with any ocular TEAEs in the study eye were also similar across all 3 treatment groups: 42.4% in the aflibercept 8 mg Q12W group, 42.3% in the aflibercept 8 mg Q16W group, and 42.3% in the pooled Q12W and Q16W treatment groups versus 45.2% in the aflibercept 2 mg Q8W group. 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 29.1%, 12.3%, and 0.9%, respectively. In the aflibercept 2 mg Q8W group, the proportions were 35.4%, 8.9%, and 0.9%, respectively (Table 19).

The proportions of patients with TEAEs related to intraocular inflammation in the study eye were low and similar across the treatment groups. Furthermore, there were no clinically relevant differences in proportions of patients with increased intraocular pressure between treatment groups; this event was present in 3.1% of patients in the pooled aflibercept 8 mg Q12W and Q16W treatment groups and 2.7% of patients in the aflibercept 2 mg Q8W group (Table 19).

Proportion of participants with any study-drug-related ocular treatment-emergent adverse events and any non-ocular treatment-emergent adverse events through week 60

The proportions of patients who experienced any study-drug-related TEAEs were similar across all 3 treatment groups and generally of low frequency: 4.4% in the aflibercept 8 mg Q16W group and 6.0% in the aflibercept 8 mg Q12W group (5.2% in the pooled Q12W and Q16W treatment groups) versus 5.4% in the aflibercept 2 mg Q8W group (Table 19). Any study-drug-related ocular TEAEs were reported in 3.8% of participants in the aflibercept 8 mg Q16W group and 5.4% of participants in the aflibercept 8 mg Q12W group (4.6% in the pooled Q12W and Q16W treatment groups) compared with 3.9% of participants in the aflibercept 2 mg Q8W group (Table 19).

Ocular TEAEs in the study eye judged to be related to study drug were generally of low frequency and mostly reported for single participants only. Ocular TEAEs in the study eye judged to be related to study drug were reported in 4.6% of participants in the pooled aflibercept 8 mg groups and in 3.6% of participants in the aflibercept 2 mg Q8W group (Table 19). The only ocular TEAEs in the study eye judged to be related to study drug that were reported for >2 participants in any treatment group were retinal pigment epithelial tear, visual acuity reduced, and increased intraocular pressure (Table 19).

Proportion of participants with any ocular treatment-emergent adverse events and any non-ocular TEAEs leading to discontinuation of the study drug through Week 60

The proportions of patients who experienced any TEAEs leading to discontinuation of a study drug were similar across all 3 treatment groups and generally of low frequency with 1.8% in the aflibercept 8 mg Q16W group, 1.5% in the aflibercept 8 mg Q12W group (1.6% in the pooled Q12W and Q16W treatment groups) versus 2.4% in the aflibercept 2 mg Q8W group (Table 19). The proportions of patients who experienced any ocular TEAEs leading to discontinuation of study drug were 1.2% in the aflibercept 8 mg Q16W group, in the aflibercept 8 mg Q12W group and in the pooled Q12W and Q16W treatment groups versus 0.6% in the aflibercept 2 mg Q8W group (Table 19).

Ocular TEAEs in the study eye that resulted in discontinuation of the study drug affected few participants (Table 19): 1.2% of patients in the pooled aflibercept 8 mg Q12W and Q16W treatment groups and 0.6% of participants in the aflibercept 2 mg Q8W group. Similarly, non-ocular TEAEs resulted in discontinuation of the study drug in 0.4% of participants in the pooled aflibercept 8 mg Q12W and Q16W treatment groups and 1.8% of participants in the aflibercept 2 mg Q8W group.

Proportion of participants with treatment-emergent adverse events related to intravitreal injection procedure in the study eye through week 60

The proportions of ocular TEAEs related to intravitreal injection procedure in the study eye were similar between the aflibercept 8 mg groups and aflibercept 2 mg group. Intravitreal injection procedure-related TEAEs in the study eye were reported in 10.5% of participants in the pooled aflibercept 8 mg groups and in 12.2% of participants in the aflibercept 2 mg Q8W group (Table 19). The most common ocular TEAEs related to intravitreal injection procedure in the study eye, reported in ≥5 participants, were increased intraocular pressure, conjunctival haemorrhage, vitreous floaters, eye pain, ocular hypertension, and sensation of foreign body (Table 19).

Proportion of participants with any ocular treatment-emergent serious adverse events and any non-ocular treatment-emergent serious adverse events through week 60

The proportion of participants with ocular TESAEs in the study eye was low in all treatment groups (Table 20). These TESAEs were reported in 2.1% of participants from each of aflibercept 8 mg (Q12W, Q16W, and the pooled Q12W and Q16W) groups and 1.2% of participants from the aflibercept 2 mg Q8W group. Most of the ocular TESAEs in the study eye were reported in single participants in any treatment group, with the following exceptions: retinal haemorrhage was reported in 2 participants in each of the aflibercept 8 mg Q12W and Q16W treatment groups (1 in the aflibercept 2 mg Q8W group), retinal detachment was reported in 2 participants in the aflibercept 8 mg Q12W group (1 in each the aflibercept 8 mg Q16W group and the aflibercept 2 mg Q8W group), and intraocular pressure increased was reported in 2 participants in the aflibercept 8 mg Q12W group (none in the aflibercept 8 mg Q16W or aflibercept 2 mg Q8W groups).

Non-ocular TESAEs were reported in 12.1% of participants in the aflibercept 8 mg Q16W group and 12.2% in the aflibercept 8 mg Q12W group (12.2% in the pooled Q12W and Q16W treatment groups) versus 15.8% in the aflibercept 2 mg Q8W group (Table 20).

Table 19: Overall summary of all adverse events through week 60

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Aflibercept 8 mg Q16W n=338	Pooled n=673
Any AE	263 (78.3%)	258 (77.0%)	278 (82.2%)	536 (79.6%)
Any pre-treatment AE	33 (9.8%)	15 (4.5%)	35 (10.4%)	50 (7.4%)
Any TEAE	260 (77.4%)	256 (76.4%)	273 (80.8%)	529 (78.6%)
Any post-treatment AE	3 (0.9%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
Any ocular TEAE	181 (53.9%)	171 (51.0%)	180 (53.3%)	351 (52.2%)
Any ocular TEAE in study eye	152 (45.2%)	142 (42.4%)	143 (42.3%)	285 (42.3%)
Eye disorders[a]	128 (38.1%)	125 (37.3%)	125 (37.0%)	250 (37.1%)
Visual acuity reduced[a]	21 (6.3%)	13 (3.9%)	20 (5.9%)	33 (4.9%)
Cataract[a]	13 (3.9%)	16 (4.8%)	15 (4.4%)	31 (4.6%)
Retinal haemorrhage[a]	15 (4.5%)	12 (3.6%)	13 (3.8%)	25 (3.7%)
Subretinal fluid[a]	12 (3.6%)	11 (3.3%)	8 (2.4%)	19 (2.8%)
Vitreous floaters[a]	13 (3.9%)	4 (1.2%)	14 (4.1%)	18 (2.7%)
Vitreous detachment[a]	5 (1.5%)	7 (2.1%)	10 (3.0%)	17 (2.5%)
Macular thickening[a]	3 (0.9%)	8 (2.4%)	7 (2.1%)	15 (2.2%)
Neovascular age-related macular degeneration[a]	2 (0.6%)	8 (2.4%)	7 (2.1%)	15 (2.2%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Q16W n=338	Pooled n=673
Conjunctival haemorrhage[a]	6 (1.8%)	8 (2.4%)	6 (1.8%)	14 (2.1%)
Dry eye[a]	8 (2.4%)	7 (2.1%)	6 (1.8%)	13 (1.9%)
Eye pain[a]	3 (0.9%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Macular oedema[a]	8 (2.4%)	2 (0.6%)	8 (2.4%)	10 (1.5%)
Age-related macular degeneration[a]	2 (0.6%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Retinal pigment epithelial tear[a]	3 (0.9%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Posterior capsule opacification[a]	1 (0.3%)	3 (0.9%)	5 (1.5%)	8 (1.2%)
Dry age-related macular degeneration[a]	5 (1.5%)	5 (1.5%)	2 (0.6%)	7 (1.0%)
Ocular hypertension[a]	1 (0.3%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
Retinal oedema[a]	4 (1.2%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
Macular fibrosis[a]	5 (1.5%)	3 (0.9%)	3 (0.9%)	6 (0.9%)
Eye irritation[a]	0	1 (0.3%)	4 (1.2%)	5 (0.7%)
Punctate keratitis[a]	5 (1.5%)	1 (0.3%)	4 (1.2%)	5 (0.7%)
Epiretinal membrane[a]	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Photopsia[a]	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Detachment of macular retinal pigment epithelium[a]	5 (1.5%)	1 (0.3%)	1 (0.3%)	2 (0.3%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Q16W n=338	Pooled n=673
Investigations[a]	10 (3.0%)	15 (4.5%)	13 (3.8%)	28 (4.2%)
Intraocular pressure increased[a]	9 (2.7%)	11 (3.3%)	10 (3.0%)	21 (3.1%)
General disorders and administration site conditions[a]	12 (3.6%)	9 (2.7%)	10 (3.0%)	19 (2.8%)
Sensation of foreign body[a]	7 (2.1%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
Infections and infestations[a]	8 (2.4%)	11 (3.3%)	4 (1.2%)	15 (2.2%)
Conjunctivitis[a]	5 (1.5%)	7 (2.1%)	3 (0.9%)	10 (1.5%)
Injury, poisoning and procedural complications[a]	8 (2.4%)	8 (2.4%)	6 (1.8%)	14 (2.1%)
Corneal abrasion[a]	4 (1.2%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
Any ocular TEAE in fellow eye	107 (31.8%)	93 (27.8%)	97 (28.7%)	190 (28.2%)
Any non-ocular TEAE	201 (59.8%)	199 (59.4%)	207 (61.2%)	406 (60.3%)
Any study-drug-related TEAE	18 (5.4%)	20 (6.0%)	15 (4.4%)	35 (5.2%)
Any study-drug-related ocular TEAE	13 (3.9%)	18 (5.4%)	13 (3.8%)	31 (4.6%)
Any study-drug-related ocular TEAE in study eye	12 (3.6%)	18 (5.4%)	13 (3.8%)	31 (4.6%)
Retinal pigment epithelial tear	1 (0.3%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Visual acuity reduced	0	3 (0.9%)	1 (0.3%)	4 (0.6%)
Intraocular pressure increased	3 (0.9%)	1 (0.3%)	2 (0.6%)	3 (0.4%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Q16W n=338	Pooled n=673
Any study-drug-related ocular TEAE in fellow eye	2 (0.6%)	0	2 (0.6%)	2 (0.3%)
Any study-drug-related non-ocular TEAE	5 (1.5%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Any TEAE related to intravitreal injection procedure	45 (13.4%)	38 (11.3%)	40 (11.8%)	78 (11.6%)
Any ocular TEAE related to intravitreal injection procedure	45 (13.4%)	37 (11.0%)	40 (11.8%)	77 (11.4%)
Any ocular TEAE related to intravitreal injection procedure in study eye	41 (12.2%)	32 (9.6%)	39 (11.5%)	71 (10.5%)
Intraocular pressure increased	7 (2.1%)	5 (1.5%)	6 (1.8%)	11 (1.6%)
Conjunctival haemorrhage	4 (1.2%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Vitreous floaters	7 (2.1%)	1 (0.3%)	6 (1.8%)	7 (1.0%)
Eye pain	3 (0.9%)	2 (0.6%)	3 (0.9%)	5 (0.7%)
Ocular hypertension	1 (0.3%)	2 (0.6%)	3 (0.9%)	5 (0.7%)
Sensation of foreign body	6 (1.8%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Any ocular TEAE related to intravitreal injection procedure in fellow eye	7 (2.1%)	5 (1.5%)	6 (1.8%)	11 (1.6%)
Any non-ocular TEAE related to intravitreal injection procedure	0	4 (1.2%)	1 (0.3%)	5 (0.7%)
Any TEAE related to protocol-required procedure	22 (6.5%)	15 (4.5%)	13 (3.8%)	28 (4.2%)
Any ocular TEAE related to protocol-required procedure	14 (4.2%)	10 (3.0%)	7 (2.1%)	17 (2.5%)
Any ocular TEAE related to protocol-required procedure in study eye	13 (3.9%)	9 (2.7%)	7 (2.1%)	16 (2.4%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Q16W n=338	Pooled n=673
Any ocular TEAE related to protocol-required procedure in fellow eye	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Any non-ocular TEAE related to protocol-required procedure	8 (2.4%)	7 (2.1%)	6 (1.8%)	13 (1.9%)
Any TEAE related to fellow eye treatment	66 (19.6%)	56 (16.7%)	71 (21.0%)	127 (18.9%)
Any ocular TEAE related to fellow eye treatment	57 (17.0%)	44 (13.1%)	54 (16.0%)	98 (14.6%)
Any ocular TEAE related to fellow eye treatment in study eye	39 (11.6%)	29 (8.7%)	30 (8.9%)	59 (8.8%)
Any ocular TEAE related to fellow eye treatment in fellow eye	47 (14.0%)	38 (11.3%)	45 (13.3%)	83 (12.3%)
Any non-ocular TEAE related to fellow eye treatment	47 (14.0%)	40 (11.9%)	53 (15.7%)	93 (13.8%)
Any serious AE	61 (18.2%)	52 (15.5%)	50 (14.8%)	102 (15.2%)
Any serious pre-treatment AE	0	0	1 (0.3%)	1 (0.1%)
Any serious TEAE	59 (17.6%)	49 (14.6%)	49 (14.5%)	98 (14.6%)
Any serious post-treatment AE	2 (0.6%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Any ocular serious TEAE	6 (1.8%)	8 (2.4%)	8 (2.4%)	16 (2.4%)
Any ocular serious TEAE in study eye	4 (1.2%)	7 (2.1%)	7 (2.1%)	14 (2.1%)
Any ocular serious TEAE in fellow eye	3 (0.9%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Any non-ocular serious TEAE	53 (15.8%)	41 (12.2%)	41 (12.1%)	82 (12.2%)
Any study-drug-related serious TEAE	4 (1.2%)	0	3 (0.9%)	3 (0.4%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Q16W n=338	Pooled n=673
Any study-drug-related ocular serious TEAE	0	0	1 (0.3%)	1 (0.1%)
Any study-drug-related ocular serious TEAE in study eye	0	0	1 (0.3%)	1 (0.1%)
Any study-drug-related ocular serious TEAE in fellow eye	0	0	0	0
Any study-drug-related non-ocular serious TEAE	4 (1.2%)	0	2 (0.6%)	2 (0.3%)
Any serious TEAE related to intravitreal injection procedure	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Any ocular serious TEAE related to intravitreal injection procedure	2 (0.6%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Any ocular serious TEAE related to intravitreal injection procedure in study eye	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Any ocular serious TEAE related to intravitreal injection procedure in fellow eye	1 (0.3%)	0	0	0
Any non-ocular serious TEAE related to intravitreal injection procedure	0	1 (0.3%)	0	1 (0.1%)
Any serious TEAE related to protocol-required procedure	0	1 (0.3%)	0	1 (0.1%)
Any ocular serious TEAE related to protocol-required procedure	0	0	0	0
Any ocular serious TEAE related to protocol-required procedure in study eye	0	0	0	0
Any ocular serious TEAE related to protocol-required procedure in fellow eye	0	0	0	0

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Q16W n=338	Pooled n=673
Any non-ocular serious TEAE related to protocol-required procedure	0	1 (0.3%)	0	1 (0.1%)
Any serious TEAE related to fellow eye treatment	16 (4.8%)	12 (3.6%)	12 (3.6%)	24 (3.6%)
Any ocular serious TEAE related to fellow eye treatment	2 (0.6%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
Any ocular serious TEAE related to fellow eye treatment in study eye	1 (0.3%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Any ocular serious TEAE related to fellow eye treatment in fellow eye	1 (0.3%)	1 (0.3%)	0	1 (0.1%)
Any non-ocular serious TEAE related to fellow eye treatment	14 (4.2%)	8 (2.4%)	10 (3.0%)	18 (2.7%)
Any TEAE with outcome death	5 (1.5%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Any pre-treatment AE with outcome death	0	0	0	0
Any post-treatment AE with outcome death	0	0	0	0
Any TEAE of intraocular inflammation in the study eye	4 (1.2%)	4 (1.2%)	1 (0.3%)	5 (0.7%)
Any Adjudicated Treatment-Emergent APTC Events	8 (2.4%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Any TEAE of hypertension	16 (4.8%)	23 (6.9%)	22 (6.5%)	45 (6.7%)
Any TEAE of nasal mucosal finding	0	0	2 (0.6%)	2 (0.3%)
Any TEAE leading to discontinuation of study drug	8 (2.4%)	5 (1.5%)	6 (1.8%)	11 (1.6%)
Any ocular TEAE leading to discontinuation of study drug[b]	2 (0.6%)	4 (1.2%)	4 (1.2%)	8 (1.2%)
Any ocular TEAE leading to discontinuation of study drug in study eye	2 (0.6%)	4 (1.2%)	4 (1.2%)	8 (1.2%)

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Q16W n=338	Pooled n=673
Any ocular TEAE leading to discontinuation of study drug in fellow eye	0	0	0	0
Any non-ocular TEAE leading to discontinuation of study drug[b]	6 (1.8%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Maximum intensity (% per treatment group)				
Missing intensity for any ocular TEAE in study eye	0	0	0	0
Mild intensity for any ocular TEAE in study eye	119 (35.4%)	95 (28.4%)	101 (29.9%)	196 (29.1%)
Moderate intensity for any ocular TEAE in study eye	30 (8.9%)	43 (12.8%)	40 (11.8%)	83 (12.3%)
Severe intensity for any ocular TEAE in study eye	3 (0.9%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
Missing intensity for any ocular TEAE in fellow eye	0	0	0	0
Mild intensity for any ocular TEAE in fellow eye	78 (23.2%)	66 (19.7%)	66 (19.5%)	132 (19.6%)
Moderate intensity for any ocular TEAE in fellow eye	27 (8.0%)	25 (7.5%)	30 (8.9%)	55 (8.2%)
Severe intensity for any ocular TEAE in fellow eye	2 (0.6%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
Missing intensity for any non-ocular TEAE	0	0	0	0
Mild intensity for any non-ocular TEAE	100 (29.8%)	111 (33.1%)	104 (30.8%)	215 (31.9%)
Moderate intensity for any non-ocular TEAE	69 (20.5%)	68 (20.3%)	88 (26.0%)	156 (23.2%)
Severe intensity for any non-ocular TEAE	32 (9.5%)	20 (6.0%)	15 (4.4%)	35 (5.2%)
Missing intensity for any ocular serious TEAE in study eye	0	0	0	0

Safety analysis set	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	Q16W n=338	Pooled n=673
Mild intensity for any ocular serious TEAE in study eye	1 (0.3%)	0	0	0
Moderate intensity for any ocular serious TEAE in study eye	1 (0.3%)	4 (1.2%)	5 (1.5%)	9 (1.3%)
Severe intensity for any ocular serious TEAE in study eye	2 (0.6%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Missing intensity for any ocular serious TEAE in fellow eye	0	0	0	0
Mild intensity for any ocular serious TEAE in fellow eye	1 (0.3%)	0	0	0
Moderate intensity for any ocular serious TEAE in fellow eye	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Severe intensity for any ocular serious TEAE in fellow eye	1 (0.3%)	0	0	0
Missing intensity for any non-ocular serious TEAE	0	0	0	0
Mild intensity for any non-ocular serious TEAE	6 (1.8%)	7 (2.1%)	3 (0.9%)	10 (1.5%)
Moderate intensity for any non-ocular serious TEAE	18 (5.4%)	14 (4.2%)	24 (7.1%)	38 (5.6%)
Severe intensity for any non-ocular serious TEAE	29 (8.6%)	20 (6.0%)	14 (4.1%)	34 (5.1%)

AE=adverse event; APTC=Anti-Platelet Trialists' Collaboration; MedDRA=Medical Dictionary for Regulatory Activities; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; 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.

Post-treatment AEs are defined as AEs that started more than 30 days after the last injection (active or sham) in the study. Of note, for 1 participant, an AE of retinal tear (retina break from laser) was recorded with a start date prior to informed consent.

Fellow-eye treatment refers to commercial aflibercept (2 mg), which was not provided by the sponsor through study medication supplies.

[a]Ocular TEAEs (preferred term MedDRA version 25.0) in the study eye occurring in > 1% of the participants in any treatment group through week 60. The threshold of > 1% was applied to any system organ class and any preferred term in any treatment group. System organ classes and preferred terms that met the threshold are sorted by decreasing order of frequency in the pooled Q12W and Q16W groups. System organ classes that met the threshold but none of the underlying preferred terms are not displayed. The number (%) of participants with ≥1 TEAE overall and in each system organ class are without consideration for the threshold.

[b]There were 6 participants who reported ≥1 TEAE resulting in discontinuation of study drug, but the reason for premature discontinuation of treatment was not recorded as an adverse event.

Source: PULSAR Clinical Study Report (week 60).

Table 20 Ocular and non-ocular TESAEs, safety analysis set week 60

Primary system organ class Preferred term MedDRA version 25.0	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	 Q16W n=338	 Pooled n=673
Ocular TESAEs in study eye				
Number (%) of subjects with ≥1 such AE	4 (1.2%)	7 (2.1%)	7 (2.1%)	14 (2.1%)
Eye disorders	3 (0.9%)	5 (1.5%)	6 (1.8%)	11 (1.6%)
Retinal haemorrhage	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Retinal detachment	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
Angle closure glaucoma	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Cataract	0	0	1 (0.3%)	1 (0.1%)
Dry age-related macular degeneration	0	1 (0.3%)	0	1 (0.1%)
Vitreous haemorrhage	0	0	1 (0.3%)	1 (0.1%)
Investigations	0	2 (0.6%)	0	2 (0.3%)
Intraocular pressure increased	0	2 (0.6%)	0	2 (0.3%)
Injury, poisoning and procedural complications	0	0	1 (0.3%)	1 (0.1%)
Skin laceration	0	0	1 (0.3%)	1 (0.1%)
Infections and infestations	1 (0.3%)	0	0	0
Endophthalmitis	1 (0.3%)	0	0	0
Non-ocular TESAEs occurring in >1 participant				
Number (%) of subjects with ≥1 such adverse event	53 (15.8%)	41 (12.2%)	41 (12.1%)	82 (12.2%)
Pneumonia	1 (0.3%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
Cellulitis	0	2 (0.6%)	0	2 (0.3%)
Pyelonephritis acute	0	0	2 (0.6%)	2 (0.3%)

Primary system organ class Preferred term MedDRA version 25.0	Aflibercept 2 mg Q8W n=336	Aflibercept 8 mg Q12W n=335	 Q16W n=338	 Pooled n=673
Urinary tract infection	4 (1.2%)	1 (0.3%)	0	1 (0.1%)
Gastric cancer	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Bladder neoplasm	3 (0.9%)	0	0	0
Angina pectoris	0	0	3 (0.9%)	3 (0.4%)
Angina unstable	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cardiac failure congestive	0	2 (0.6%)	0	2 (0.3%)
Osteoarthritis	1 (0.3%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Back pain	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Chronic obstructive pulmonary disease	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Syncope	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cerebrovascular accident	2 (0.6%)	1 (0.3%)	0	1 (0.1%)
Cerebral infarction	2 (0.6%)	0	0	0
Chest pain	0	2 (0.6%)	1 (0.3%)	3 (0.4%)
Hypertension	1 (0.3%)	2 (0.6%)	0	2 (0.3%)
Pelvic fracture	2 (0.6%)	0	0	0
Rib fracture	2 (0.6%)	0	0	0
Upper limb fracture	2 (0.6%)	0	0	0
Hyponatraemia	2 (0.6%)	0	2 (0.6%)	2 (0.3%)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TESAE=treatment-emergent serious 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.

System organ classes and preferred terms are sorted by decreasing order of frequency in the pooled aflibercept 8 mg Q12W and Q16W groups.

Source: PULSAR Clinical Study Report (week 60).

PULSAR study: 96-week safety results (Ocular TEAE/ocular/non-ocular TESAE) for aflibercept 8 mg were similar to aflibercept 2 mg

The latest data cut for 96 weeks safety data is displayed below in Table 21, Table 22 and Table 23 which shows similar safety data across 2 mg and 8 mg aflibercept.

Table 21 Overall summary of adverse events for 96-week (safety analysis set)

	Q8W N= 336	Q12W N= 335	Q16W N=338	All HD N=673
Any AE with outcome death	12 (3.6%)	10 (3.0%)	7 (2.1%)	17 (2.5%)
Any pre-treatment AE with outcome death	0	0	0	0
Any TEAE with outcome death	9 (2.7%)	10 (3.0%)	4 (1.2%)	14 (2.1%)
Any post-treatment AE with outcome death	3 (0.9%)	0	3 (0.9%)	3 (0.4%)
Any TEAE of intraocular inflammation in the study eye	7 (2.1%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Any Adjudicated Treatment-Emergent APTC Events	18 (5.4%)	24 (7.2%)	15 (4.4%)	39 (5.8%)
Any TEAE of hypertension	27 (8.0%)	27 (8.1%)	28 (8.3%)	55 (8.2%)
Any TEAE of nasal mucosal finding	0	0	3 (0.9%)	3 (0.4%)

Table 22 Ocular TEAE of the study eye, 96-week safety results

	Q8W N=336	Q12W N=335	Q16W N=338	All HD N=673
Eye disorders				
▪ Keratic precipitates	0	0	1 (0.3%)	1 (0.1%)
▪ Lacrimation increased	0	0	1 (0.3%)	1 (0.1%)
▪ Macular degeneration	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
▪ Macular fibrosis	4 (1.2%)	3 (0.9%)	3 (0.9%)	6 (0.9%)
▪ Macular hole	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
▪ Macular oedema	8 (2.4%)	1 (0.3%)	7 (2.1%)	8 (1.2%)
▪ Macular scar	0	0	1 (0.3%)	1 (0.1%)

▪ Macular thickening	3 (0.9%)	7 (2.1%)	6 (1.8%)	13 (1.9%)
▪ Maculopathy	0	0	1 (0.3%)	1 (0.1%)
▪ Meibomian gland dysfunction	2 (0.6%)	2 (0.6%)	0	2 (0.3%)
▪ Metamorphopsia	1 (0.3%)	0	0	0
▪ Narrow anterior chamber angle	0	1 (0.3%)	0	1 (0.1%)
▪ Neovascular age-related macular degeneration	2 (0.6%)	7 (2.1%)	7 (2.1%)	14 (2.1%)
▪ Ocular discomfort	3 (0.9%)	1 (0.3%)	0	1 (0.1%)
▪ Ocular hyperaemia	2 (0.6%)	0	0	0
▪ Ocular hypertension	1 (0.3%)	2 (0.6%)	4 (1.2%)	6 (0.9%)
▪ Ocular surface disease	0	0	1 (0.3%)	1 (0.1%)
▪ Optic disc drusen	0	0	1 (0.3%)	1 (0.1%)
▪ Papilloedema	0	0	1 (0.3%)	1 (0.1%)
▪ Periorbital pain	0	1 (0.3%)	0	1 (0.1%)
▪ Photophobia	0	0	2 (0.6%)	2 (0.3%)
▪ Photopsia	3 (0.9%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
▪ Posterior capsule opacification	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Infections and infestations	0	1 (0.3%)	0	1 (0.1%)
▪ Conjunctivitis	0	1 (0.3%)	0	1 (0.1%)
Injury, poisoning and procedural complications	3 (0.9%)	0	2 (0.6%)	2 (0.3%)
▪ Corneal abrasion	3 (0.9%)	0	1 (0.3%)	1 (0.1%)
▪ Skin laceration	0	0	1 (0.3%)	1 (0.1%)
Investigations	4 (1.2%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
▪ Intraocular pressure increased	4 (1.2%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Nervous system disorders	0	1 (0.3%)	0	1 (0.1%)
▪ Headache	0	1 (0.3%)	0	1 (0.1%)
Surgical and medical procedures	0	1 (0.3%)	0	1 (0.1%)

▪ Ophthalmic fluid-air exchange procedure	0	1 (0.3%)	0	1 (0.1%)

Table 23 Ocular treatment emergent serious adverse events: number of subjects by primary system organ class and preferred term

	Q8W n=336	Q12W n=335	Q16W n=338	All HD n=673
Number (%) of subjects with at least one such adverse event in the study eye	**4 (1.2%)**	**10 (3.0%)**	**10 (3.0%)**	**20 (3.0%)**
Eye disorders	**3 (0.9%)**	**8 (2.4%)**	**9 (2.7%)**	**17 (2.5%)**
▪ Angle closure glaucoma	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
▪ Cataract	0	2 (0.6%)	2 (0.6%)	4 (0.6%)
▪ Dry age-related macular degeneration	0	1 (0.3%)	0	1 (0.1%)
▪ Macular detachment	0	1 (0.3%)	0	1 (0.1%)
▪ Retinal detachment	1 (0.3%)	2 (0.6%)	3 (0.9%)	5 (0.7%)
▪ Retinal haemorrhage	1 (0.3%)	2 0.6%)	2 (0.6%)	4 (0.6%)
▪ Retinal tear	0	0	1 (0.3%)	1 (0.1%)
▪ Vitreous haemorrhage	0	0	1 (0.3%)	1 (0.1%)
Infections and infestations	**1 (0.3%)**	**0**	**0**	**0**
▪ Endophthalmitis	1 (0.3%)	0	0	0
Injury, poisoning and procedural complications	0	0	1 (0.3%)	1 (0.1%)
▪ Skin laceration	0	0	1 (0.3%)	1 (0.1%)
Investigations	0	2 (0.6%)	0	2 (0.3%)
▪ Intraocular pressure increased	0	2 (0.6%)	0	2 (0.3%)
	Q8W n=336	**Q12W n=335**	**Q16W n=338**	**All HD n=673**
Number (%) of subjects with at least one non-ocular adverse event	**66 (19.6%)**	**73 (21.8%)**	**64 (18.9%)**	**137 (20.4%)**
Blood and lymphatic system disorders	**2 (0.6%)**	**2 (0.6%)**	**0**	**2 (0.3%)**
▪ Anaemia	1 (0.3%)	1 (0.3%)	0	1 (0.1%)
▪ Blood loss anaemia	1 (0.3%)	0	0	0
▪ Hypochromic anaemia	0	1 (0.3%)	0	1 (0.1%)
Cardiac disorders	**10 (3.0%)**	**16 (4.8%)**	**12 (3.6%)**	**28 (4.2%)**
▪ Acute coronary syndrome	1 (0.3%)	0	0	0

▪ Acute left ventricular failure	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
▪ Acute myocardial infarction	2 (0.6%)	1 (0.3%)	0	1 (0.1%)
▪ Angina pectoris	1 (0.3%)	0	4 (1.2%)	4 (0.6%)
▪ Angina unstable	0	2 (0.6%)	1 (0.3%)	3 (0.4%)
▪ Aortic valve stenosis	0	1 (0.3%)	0	1 (0.1%)
▪ Arrhythmia	0	1 (0.3%)	0	1 (0.1%)
▪ Arteriosclerosis coronary artery	0	1 (0.3%)	0	1 (0.1%)
▪ Atrial fibrillation	1 (0.3%)	2 (0.6%)	0	2 (0.3%)
▪ Bradycardia	1 (0.3%)	0	0	0
▪ Cardiac arrest	1 (0.3%)	0	0	0
▪ Cardiac failure	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
▪ Cardiac failure chronic	0	1 (0.3%)	0	1 (0.1%)
▪ Cardiac failure congestive	0	3 (0.9%)	0	3 (0.4%)
▪ Coronary artery disease	0	2 (0.6%)	1 (0.3%)	3 (0.4%)

	Q8W n=336	Q12W n=335	Q16W n=338	All HD n= 673
Cardiac disorders				
▪ Coronary artery stenosis	0	2 (0.6%)	0	2 (0.3%)
▪ Myocardial infarction	1 (0.3%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
▪ Myocardial ischaemia	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Ear and labyrinth disorders	**0**	**1 (0.3%)**	**1 (0.3%)**	**2 (0.3%)**
▪ Tinnitus	0	0	1 (0.3%)	1 (0.1%)
▪ Vertigo	0	1 (0.3%)	0	1 (0.1%)
Endocrine disorders	**0**	**0**	**1 (0.3%)**	**1 (0.1%)**
▪ Goitre	0	0	1 (0.3%)	1 (0.1%)

	Q8W n=336	Q12W n=335	Q16W n=338	All HD n=673
Gastrointestinal disorders	**7 (2.1%)**	**11 (3.3%)**	**7 (2.1%)**	**18 (2.7%)**
▪ Abdominal pain	1 (0.3%)	0	0	0
▪ Abdominal pain upper	0	0	1 (0.3%)	1 (0.1%)
▪ Abdominal strangulated hernia	1 (0.3%)	0	0	0
▪ Colitis	0	1 (0.3%)	0	1 (0.1%)
▪ Colitis ischaemic	1 (0.3%)	0	0	0
▪ Diarrhoea	0	2 (0.6%)	0	2 (0.3%)

▪ Dysphagia	0	0	1 (0.3%)	1 (0.1%)
▪ Enteritis	1 (0.3%)	1 (0.3%)	0	1 (0.1%)
▪ Intestinal obstruction	0	2 (0.6%)	0	2 (0.3%)
▪ Large intestine polyp	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
▪ Mechanical ileus	0	1 (0.3%)	0	1 (0.1%)
▪ Mesenteric artery thrombosis	0	1 (0.3%)	0	1 (0.1%)
▪ Nausea	0	0	1 (0.3%)	1 (0.1%)
▪ Oesophageal stenosis	0	1 (0.3%)	0	1 (0.1%)
▪ Oesophagitis	1 (0.3%)	0	0	0
▪ Pancreatitis	0	1 (0.3%)	0	1 (0.1%)
▪ Pancreatitis chronic	0	0	1 (0.3%)	1 (0.1%)
▪ Small intestinal perforation	0	0	1 (0.3%)	1 (0.1%)
▪ Umbilical hernia	0	0	1 (0.3%)	1 (0.1%)
▪ Upper gastrointestinal haemorrhage	1 (0.3%)	0	0	0

	Q8W n=336	Q12W n=335	Q16W n=338	All HD n= 673
General disorders and administration site conditions	**1 (0.3%)**	**5 (1.5%)**	**6 (1.8%)**	**11 (1.6%)**
▪ Asthenia	0	0	1 (0.3%)	1 (0.1%)
▪ Chest pain	0	2 (0.6%)	1 (0.3%)	3 (0.4%)
▪ Cyst	0	0	1 (0.3%)	1 (0.1%)
▪ Death	0	1 (0.3%)	2 (0.6%)	3 (0.4%)
▪ Oedema	0	1 (0.3%)	0	1 (0.1%)
▪ Pain	0	1 (0.3%)	0	1 (0.1%)
▪ Peripheral swelling	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
▪ Hepatobiliary disorders	3 (0.9%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
▪ Bile duct stone	1 (0.3%)	0	0	0
▪ Cholangitis	0	1 (0.3%)	0	1 (0.1%)
▪ Cholecystitis	2 (0.6%)	0	0	0
▪ Cholelithiasis	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
▪ Hepatic vascular thrombosis	0	0	1 (0.3%)	1 (0.1%)
Infections and infestations	**9 (2.7%)**	**11 (3.3%)**	**22 (6.5%)**	**33 (4.9%)**
▪ Appendicitis	0	0	2 (0.6%)	2 (0.3%)
▪ Bronchitis	0	0	1 (0.3%)	1 (0.1%)

▪ COVID-19	0	0	2 (0.6%)	2 (0.3%)
▪ COVID-19 pneumonia	0	1 (0.3%)	0	1 (0.1%)
▪ Cellulitis	0	2 (0.6%)	0	2 (0.3%)
▪ Diverticulitis	0	1 (0.3%)	0	1 (0.1%)

	Q8W n=336	Q12W n=335	Q16W n=338	All HD n= 673
Injury, poisoning and procedural complications	**13 (3.9%)**	**3 (0.9%)**	**3 (0.9%)**	**6 (0.9%)**
▪ Fall	1 (0.3%)	0	0	0
▪ Femoral neck fracture	1 (0.3%)	0	0	0
▪ Femur fracture	1 (0.3%)	0	0	0
▪ Hip fracture	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
▪ Ligament sprain	0	1 (0.3%)	0	1 (0.1%)
▪ Patella fracture	1 (0.3%)	0	0	0
▪ Pelvic fracture	2 (0.6%)	0	0	0
▪ Post procedural haemorrhage	1 (0.3%)	0	0	0
▪ Postoperative wound complication	0	1 (0.3%)	0	1 (0.1%)
▪ Rib fracture	2 (0.6%)	0	0	0
▪ Shoulder fracture	1 (0.3%)	0	0	0
▪ Skull fracture	1 (0.3%)	0	0	0
▪ Spinal compression fracture	1 (0.3%)	0	2 (0.6%)	2 (0.3%)
▪ Thoracic vertebral fracture	1 (0.3%)	0	0	0
▪ Upper limb fracture	1 (0.3%)	0	0	0
▪ Wrist fracture	0	1 (0.3%)	0	1 (0.1%)
Metabolism and nutrition disorders	**4 (1.2%)**	**1 (0.3%)**	**2 (0.6%)**	**3 (0.4%)**
▪ Hyperglycaemia	1 (0.3%)	1 (0.3%)	0	1 (0.1%)
▪ Hypokalaemia	1 (0.3%)	0	0	0
▪ Hyponatraemia	2 (0.6%)	0	2 (0.6%)	2 (0.3%)
▪ Malnutrition	1 (0.3%)	0	0	0

	Q8W n=336	Q12W n=335	Q16W n=338	All HD n= 673
Infections and infestations				
▪ Erysipelas	0	1 (0.3%)	0	1 (0.1%)
▪ Gangrene	0	0	1 (0.3%)	1 (0.1%)
▪ Herpes zoster	0	1 (0.3%)	0	1 (0.1%)

▪ Infective exacerbation of chronic obstructive airways disease	0	0	1 (0.3%)	1 (0.1%)
▪ Liver abscess	0	0	1 (0.3%)	1 (0.1%)
▪ Otitis externa	0	1 (0.3%)	0	1 (0.1%)
▪ Pneumonia	2 (0.6%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
▪ Pneumonia aspiration	1 (0.3%)	0	0	0
▪ Pneumonia viral	0	0	1 (0.3%)	1 (0.1%)
▪ Pyelonephritis	0	0	1 (0.3%)	1 (0.1%)
▪ Pyelonephritis acute	0	0	2 (0.6%)	2 (0.3%)
▪ Q fever	0	0	1 (0.3%)	1 (0.1%)
▪ Sepsis	0	0	1 (0.3%)	1 (0.1%)
▪ Sinusitis	1 (0.3%)	0	0	0
▪ Staphylococcal sepsis	0	0	1 (0.3%)	1 (0.1%)
▪ Systemic infection	0	0	1 (0.3%)	1 (0.1%)
▪ Urinary tract infection	5 (1.5%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
▪ Urosepsis	1 (0.3%)	0	0	0

	Q8W n=336	Q12W n=335	Q16W n=338	All HD n= 673
Renal and urinary disorders	**5 (1.5%)**	**2 (0.6%)**	**1 (0.3%)**	**3 (0.4%)**
▪ Acute kidney injury	1 (0.3%)	1 (0.3%)	0	1 (0.1%)
▪ Bladder stenosis	1 (0.3%)	0	0	0
▪ Cystitis haemorrhagic	1 (0.3%)	0	0	0
▪ Renal cyst	1 (0.3%)	0	0	0
▪ Renal impairment	0	1 (0.3%)	0	1 (0.1%)
▪ Renal mass	1 (0.3%)	0	0	0
▪ Ureterolithiasis	0	0	1 (0.3%)	1 (0.1%)
Reproductive system and breast disorders	**1 (0.3%)**	**1 (0.3%)**	**0**	**1 (0.1%)**
▪ Cervical dysplasia	0	1 (0.3%)	0	1 (0.1%)
▪ Prostatitis	1 (0.3%)	0	0	0

	Q8W n=336	Q12W n=335	Q16W n=338	All HD n= 673
Vascular disorders	**2 (0.6%)**	**4 (1.2%)**	**0**	**4 (0.6%)**
▪ Giant cell arteritis	1 (0.3%)	0	0	0
▪ Hypertension	1 (0.3%)	2 (0.6%)	0	2 (0.3%)

▪ Hypotension	0	1 (0.3%)	0	1 (0.1%)
▪ Venous thrombosis limb	0	1 (0.3%)	0	1 (0.1%)

	Q8W n=336	Q12W n=335	Q16W n=338	All HD n= 673
Number (%) of subjects with at least one such adverse event	**4 (1.2%)**	**0**	**3 (0.9%)**	**3 (0.4%)**
▪ Cardiac disorders	1 (0.3%)	0	2 (0.6%)	2 (0.3%)
▪ Acute myocardial infarction	1 (0.3%)	0	0	0
▪ Myocardial infarction	0	0	2 (0.6%)	2 (0.3%)
▪ Nervous system disorders	2 (0.6%)	0	0	0
▪ Cerebrovascular accident	2 (0.6%)	0	0	0
▪ Respiratory, thoracic and mediastinal disorders	0	0	1 (0.3%)	1 (0.1%)
▪ Pulmonary embolism	0	0	1 (0.3%)	1 (0.1%)
▪ Vascular disorders	1 (0.3%)	0	0	0
▪ Hypertension	1 (0.3%)	0	0	0

5.2.3 Method of synthesis

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

5.2.4 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.

6. References

1. Royal College of Ophthalmologists. Commissioning Guidance: Age Related Macular Degeneration Services. London: Royal College of Ophthalmologists; 2021.

2. Summary of product characteristics. Eylea 2mg (aflibercept): European Medicines Agency (EMA); 2022 [Available from: https://www.ema.europa.eu/en/documents/product-information/eylea-epar-product-information_en.pdf].

3. Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi MP, Shi E, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis. 2012;15(2):171-85.

4. Ohno-Matsui K, Hirose A, Yamamoto S, Saikia J, Okamoto N, Gehlbach P, et al. Inducible expression of vascular endothelial growth factor in adult mice causes severe proliferative retinopathy and retinal detachment. Am J Pathology. 2002;160(2):711-9.

5. Flaxel CJ, Adelman RA, Bailey ST, Fawzi A, Lim JI, Vemulakonda GA, et al. Age-Related Macular Degeneration Preferred Practice Pattern®. Ophthalmology. 2020;127(1):P1-65.

6. Schmidt-Erfurth U, Chong V, Loewenstein A, Larsen M, Souied E, Schlingemann R, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol. 2014;98(9):1144-67.

7. Saishin Y, Saishin Y, Takahashi K, Lima e Silva R, Hylton D, Rudge JS, et al. VEGF-TRAP(R1R2) suppresses choroidal neovascularization and VEGF-induced breakdown of the blood-retinal barrier. J Cell Physiology. 2003;195(2):241-8.

8. Krzystolik MG, Afshari MA, Adamis AP, Gaudreault J, Gragoudas ES, Michaud NA, et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Opthalmol. 2002;120(3):338-

9. Kwak N, Okamoto N, Wood JM, Campochiaro PA. VEGF is major stimulator in model of choroidal neovascularization. Invest Opthalmol Vis Sci. 2000;41(10):3158-64.

10. Rakic JM, Lambert V, Devy L, Luttun A, Carmeliet P, Claes C, et al. Placental growth factor, a member of the VEGF family, contributes to the development

of choroidal neovascularization. Invest Opthalmol Vis Sci. 2003;44(7):3186-93.

Appendix A. Main characteristics of studies included

Table 24 Main characteristic of studies included

Trial name: PULSAR	NCT number: NCT04423718
Objective	The primary objective of the study was to determine if treatment with aflibercept 8 mg at intervals of 12 or 16 weeks (both after 3 initial injections at 4-week intervals) provides non-inferior BCVA change compared with aflibercept 2 mg every 8 weeks (after 3 initial injections at 4-week intervals) in participants with nAMD.
Publications – title, author, journal, year	Submitted for publication
Study type and design	PULSAR is an ongoing phase 3, multicentre, randomised, double-masked, active-controlled study investigating the efficacy, safety, and tolerability of intravitreal administration of aflibercept 8 mg compared with aflibercept 2 mg in treatment-naïve patients with nAMD. The primary objective of the study was to determine if treatment with aflibercept 8 mg at intervals of 12 or 16 weeks (both after 3 initial injections at 4-week intervals) provides non-inferior BCVA change compared with aflibercept 2 mg every 8 weeks (after 3 initial injections at 4-week intervals) in participants with nAMD. The secondary objectives were to determine the effect of aflibercept 8 mg versus 2 mg aflibercept on functional and anatomic measures of response as well as on vision-related quality of life and to evaluate the safety and tolerability of aflibercept 8 mg. The ongoing masked part of the study (up to week 96) consists of a 3-week screening period, a treatment period of 92 weeks, and an end-of-study visit at week 96. An extension study with aflibercept 8 mg in all treatment groups starts immediately after the last scheduled procedure at the end of the week-96 study visit and consists of a transition period of 12 weeks (week 96 to week 108), during which the study drug is still administered in a masked fashion, followed by an open-label treatment period of 48 weeks, and an end-of-study visit at week 156. The study is being conducted at 251 sites in 27 countries or regions in Europe, North America, Latin America, Australia, and Asia Pacific. Of the

total sample size of approximately 960 participants, at least 96 (10%) were planned to be enrolled in Japan to provide consistent results with a certain probability as required by Japanese Pharmaceuticals and Medical Devices Agency (PMDA) guidelines.

Participants were randomly assigned in a 1:1:1 ratio to 1 of 3 parallel treatment groups:

- Aflibercept 2 mg administered every 8 weeks (Q8W), after 3 initial injections at 4-week intervals [as indicated in label (99)]
- Aflibercept 8 mg administered every 12 weeks (Q12W), after 3 initial injections at 4-week intervals
- Aflibercept 8 mg administered every 16 weeks (Q16W), after 3 initial injections at 4-week intervals

Randomisation was stratified by geographic region (Japan vs rest of world) and baseline BCVA (<60 vs ≥60) to ensure balanced distribution of the treatment groups within each stratum.

Only 1 eye could be treated in the study. The study used a double-masked design, with sham procedures at visits where active study intervention was not scheduled, to prevent participant and investigator bias during assessment of the safety and effectiveness of treatment.

Assessments for dose-regimen modifications (DRMs) were performed in all participants treated with aflibercept 8 mg at all visits beginning at week 16. Based on these assessments, participants in the aflibercept 8 mg groups might have had their treatment intervals shortened (year 1 and year 2) or extended (year 2). The minimum interval between injections was 8 weeks, which was considered a rescue regimen for participants randomised to aflibercept 8 mg and unable to tolerate a dosing interval longer than every 8 weeks. Participants in the aflibercept 2 mg group remained on fixed Q8W dosing throughout the study.

During the first year, beginning at week 16 (after 3 loading monthly doses), participants assigned to aflibercept 8 mg Q12W or Q16W had the dosing interval shortened if either of the following criteria was met:

- A participant in the aflibercept 8 mg Q12W or Q16W group met DRM criteria at week 16 or week 20 and was dosed with aflibercept 8 mg at that visit and subsequently continued receiving aflibercept 8 mg Q8W
- A participant in the aflibercept 8 mg Q16W group who had not met DRM criteria at week 16 or week 20 and met DRM criteria at week 24 was dosed with aflibercept 8 mg at that visit and subsequently continued receiving aflibercept 8 mg Q12W

Subsequently, participants who met DRM criteria at any active treatment visit had their intervals shortened by 4 weeks, to a minimum interval of 8 weeks.

During year 2, starting at week 52, all participants randomised to aflibercept 8 mg Q12W or Q16W were eligible for adjustments of their treatment intervals (shortening or extension) based on pre-specified DRM criteria, with the dose interval adjustments becoming effective at or after week 60 (after data collection for key secondary efficacy endpoint).

Dose-regimen modification criteria in PULSAR study

Dosing interval[a]	Study period	DRM criteria
Shortened dosing interval[b]	Baseline to week 96	**1.** BCVA loss >5 letters from week 12, AND **2.** >25 µm increase in CRT from week 12 OR new foveal haemorrhage OR new foveal neovascularisation
Extended dosing interval[c]	Week 52 to week 96	**1.** BCVA loss <5 letters from week 12, AND **2.** No fluid at the central subfield on OCT, AND **3.** No new onset foveal haemorrhage OR foveal neovascularisation

BCVA=best corrected visual acuity; CRT=central retinal thickness; DRM=dose regimen modification; OCT=optical coherence tomography.

[a]For participants who did not meet the criteria for shortening or extension of the interval, the dosing interval was maintained.

[b]Dosing interval shortened if both DRM criteria met.

[c]Interval extension if the above-mentioned DRM criteria were met at visits with active injection.

Trial name: PULSAR	NCT number: NCT04423718
	Q8W=aflibercept 2 mg every 8 weeks (Q8W); BCVA=best corrected visual acuity; E-DRM=dose regimen modification criteria for extension period; EMA=European Medicines Agency; HD=high dose (i.e., aflibercept 8 mg); IRF=intraretinal fluid; N=total number of participants; n=number of participants per group; nAMD=neovascular (wet) age-related macular degeneration; PMDA=Pharmaceuticals and Medical Devices Agency; SRF=subretinal fluid; q12=every 12 weeks (Q12W); q16=every 16 weeks (Q16W) Source: PULSAR Clinical Study Protocol.
Sample size (n)	960
Main inclusion criteria	• Active subfoveal CNV secondary to nAMD, including juxtafoveal lesions that affect the fovea as assessed in the study eye. • Total area of CNV (including both classic and occult components) must comprise greater than 50% of the total lesion area in the study eye. • BCVA ETDRS letter score of 78 to 24 (corresponding to a Snellen equivalent of approximately 20/32 to 20/320) in the study eye. • Decrease in BCVA determined to be primarily the result of nAMD in the study eye. • Presence of IRF and/or SRF affecting the central subfield of the study eye on OCT. • Contraceptive use by men or women should be consistent with local regulations regarding the methods of highly effective contraception for those participating in clinical studies. • Other protocol-specified inclusion criteria. • Additional inclusion criteria for Year 3: • At least one BCVA value and one central subfield retinal thickness (CST) value from measurements at one of the following visits: Visit 24 (Week 84), Visit 25 (Week 88) or Visit 26 (Week 92). • Participant is enrolled at a site that participates in the extension period.
Main exclusion criteria	• Causes of CNV other than nAMD in the study eye. • Scar, fibrosis, or atrophy involving the central subfield in the study eye. • Presence of retinal pigment epithelial tears or rips involving the central subfield in the study eye. • Uncontrolled glaucoma (defined as IOP >25 mmHg despite treatment with anti-glaucoma medication) in the study eye. • History of idiopathic or autoimmune uveitis in the study eye. • Myopia of a spherical equivalent of at least 8 diopters in the study eye prior to any refractive or cataract surgery. • History or clinical evidence of diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than nAMD in either eye. • Evidence of extraocular or periocular infection or inflammation (including infectious blepharitis, keratitis, scleritis, or conjunctivitis) in either eye at the time of screening/randomization.

Trial name: PULSAR		NCT number: NCT04423718
	• Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg). • Any prior or concomitant ocular (in the study eye) or systemic treatment (with an investigational or approved, anti-VEGF or other agent) or surgery for nAMD, except dietary supplements or vitamins. • Other protocol-specified exclusion criteria	
Intervention	Aflibercept 8 mg administered every 12 weeks (Q12W), after 3 initial injections at 4-week intervals (n=320) Aflibercept 8 mg administered every 16 weeks (Q16W), after 3 initial injections at 4-week intervals (n=320)	
Comparator(s)	Aflibercept 2 mg administered every 8 weeks (Q8W), after 3 initial injections at 4-week intervals [as indicated in label (n=320)	
Follow-up time	At week 48, 60, 96 and 156.	
Primary, secondary and exploratory endpoints	**Primary endpoint**	• Change from baseline in BCVA, measured by ETDRS letter score at week 48
	Key secondary efficacy endpoints - hierarchised criteria	• Change from baseline in BCVA, measured by ETDRS letter score at week 60 (EP-SAP only) • Proportion of participants with no IRF and no SRF in central subfield at week 16
	Secondary safety endpoint	• TEAEs and SAEs through weeks 48, 60, and 96, and through week 156
	Additional secondary efficacy endpoints	• Proportion of participants gaining ≥15 letters in BCVA from baseline at week 48 • Proportion of participants achieving an ETDRS letter score of ≥69 (approximate 20/40 Snellen equivalent) at week 48 • Change in CNV size from baseline to week 48 • Change in total lesion area from baseline to week 48 • Proportion of participants with no IRF and no SRF in the central subfield at week 48 • Change from baseline in CST at week 48 • Change from baseline in NEI VFQ-25 total score at week 48
	Exploratory efficacy endpoints	• Change from baseline in BCVA averaged over the period from week 36 to week 48 and from week 48 to week 60

		• Proportion of participants gaining ≥15 letters in BCVA from baseline at week 60 • Proportion of participants achieving an ETDRS letter score of ≥69 (approximate 20/40 Snellen equivalent) at week 60 • Proportions of participants gaining and losing ≥5 or ≥10 letters in BCVA from baseline at week 48 and week 60 • Proportion of participants losing ≥15 letters in BCVA from baseline at week 48 and week 60 • Change in CNV size from baseline to week 60 • Change in total lesion area from baseline to week 60 • Change from baseline in CST at week 60 • Proportion of participants without retinal fluid (total fluid, IRF, and/or SRF) and subRPE in central subfield at week 48 and week 60 • Time to fluid-free retina over 48 weeks and 60 weeks (total fluid, IRF, and/or SRF in the central subfield) • Proportion of participants with sustained fluid-free retina over 48 weeks and 60 weeks (total fluid, IRF, and/or SRF in the central subfield) • Change from baseline in NEI-VFQ-25 total score at week 60 • Proportion of participants without leakage on FA at week 48 and week 60
	Endpoints included in this application: Change from baseline in BCVA, measured by ETDRS letter score at week 48 and 60 Proportion of participants with no IRF and no SRF in central subfield at week 16 Proportion of participants losing ≥15 letters in BCVA from baseline at week 48 and week 60 Change from baseline in NEI VFQ-25 total score at week 48 TEAEs and TESAEs through weeks 48, 60, and 96	
Method of analysis	The primary and key secondary efficacy variables were evaluated on both the full analysis set (FAS) and the per-protocol set (PPS). The	

primary analysis was performed on the FAS and repeated on the PPS as a supplementary analysis. Safety variables were analysed using the safety analysis set (SAF).

- The FAS included all participants who had been randomly assigned to study treatment and who received ≥1 dose of study treatment. Participants were analysed within their original randomized group

- The PPS included all participants in the FAS who did not have any violation of relevant inclusion/exclusion criteria, had a baseline BCVA value available, had ≥1 post-baseline BCVA value available, and had any IRF or SRF affecting the central subfield at baseline according to the definitions described in the study's statistical analysis plan

- The SAF included all participants who were randomly assigned to study treatment and who received ≥1 dose of study treatment.

The estimand of primary interest will mainly be based on a hypothetical strategy. It describes the change from baseline for all participants that started treatment assuming all participants have stayed on treatment until Week 48.

The estimand is specified through the following definitions of population, variable, treatment condition, intercurrent events, and population-level summary:

Target population: Defined by the inclusion/exclusion criteria.

Variable: Absolute change from baseline to Week 48 in BCVA.

Treatment condition: HD aflibercept administered Q12W with option for DRM/rescue regimen, or Q16W with option for DRM/rescue regimen, versus aflibercept 2 mg administered Q8W.

Intercurrent events (ICE): Premature discontinuation from treatment (handled by hypothetical strategy). Details for other potential ICEs are given in the Table 9–12 in Appendix 9.5. Shortening/extension of the dosing interval (DRM/rescue regimen) will

	not be considered an ICE, but as part of the randomized treatment regimen. Population-level summary: Difference in least squares (LS) mean change from baseline to Week 48 in BCVA between Q12W and Q8W (Q16W and Q8W, respectively). The following 2 hypotheses will be tested in the primary analysis, to assess non-inferiority in the primary endpoint: •Q12W is non-inferior to Q8W regarding the mean change in BCVA from baseline to Week 48 using a non-inferiority margin of 4 letters. •Q16W is non-inferior to Q8W regarding the mean change in BCVA from baseline to Week 48 using a non-inferiority margin of 4 letters. Mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate and treatment group (Q16W vs. Q8W and Q12W vs. Q8W), visit and the stratification variables (geographic region [Japan vs. Rest of World] and baseline BCVA [<60 vs. ≥60]) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit. In line with the definition of estimands (see above), the primary analysis will be performed on the FAS and participants will be analyzed within their original randomized group (regardless of any changes to dose interval).
Subgroup analyses	Subgroups for efficacy analyses were: • Age at enrollment: < 65 years, ≥ 65 to < 75 years, ≥ 75 years to < 80 years, ≥ 80 years to < 85 years, ≥ 85 years • Sex: male, female • Geographic region: Japan, Rest of the world • Ethnicity: Not Hispanic or Latino, Hispanic or Latino • Race (only subgroups with sufficient sample size): White, Asian • Baseline BCVA: ≤ 73 letters, > 73 letters • Baseline PCV: yes, no Analyses of subgroups were pre-specified, descriptive only and based on FAS. Statistical testing / calculation of p-values were done for exploratory purpose.

Trial name: PULSAR		NCT number: NCT04423718
Other relevant information	Not applicable	

Appendix B. Efficacy results per study

Results per study

Results of PULSAR NCT04423718											
				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 estimand of primary interest will mainly be based on a hypothetical strategy. It describes the change from baseline for all participants that started treatment assuming all participants have stayed on treatment until Week 48.	
Week 48	AFL 2mg q8w	336	7.03 (5.57 - 8.49)							The estimand is specified through the following definitions of population, variable, treatment condition, intercurrent events, and population-level summary:	
	AFL 8mg q12w	335	6.06 (4.55 - 7.56)	-0.97	-2.87 - 0.92	0.0009					
	AFL 8mg q16w	338	5.89 (4.47 - 7.32)	-1.14	-2.97 – 0.69	0.0011					
Week 60	AFL 2mg q8w	336	7.23 (5.90 – 8.56)							Target population: Defined by the inclusion/exclusion criteria.	
	AFL 8mg q12w	335	6.37 (4.91 – 7.82)	-0.86	-2.57 - 0.84	0.0002				Variable: Absolute change from baseline to Week 48 in BCVA.	
	AFL 8mg q16w	338	6.31 (5.01 – 7.60)	-0.92	-2.51 - 0.66	<0.0001					

Results of PULSAR NCT04423718											
				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 96	AFL 2mg q8w	336	6.60 (5.17-8.03)							Treatment condition: HD aflibercept administered Q12W with option for DRM/rescue regimen, or Q16W with option for DRM/rescue regimen, versus aflibercept 2 mg administered Q8W. Intercurrent events (ICE): Premature discontinuation from treatment (handled by hypothetical strategy). Details for other potential ICEs are given in the Table 9–12 in Appendix 9.5. Shortening/extension of the dosing interval (DRM/rescue regimen) will not be considered an ICE, but as part of the randomized treatment regimen. Population-level summary: Difference in least squares (LS) mean change from baseline to Week 48 in BCVA between Q12W and Q8W (Q16W and Q8W, respectively). The following 2 hypotheses will be tested in the primary analysis, to	
	AFL 8mg q12w	335	5.59 (4.08-7.10)	-1.01	-2.82 – 0.80	0.0006					
	AFL 8mg q16w	338	5.52 (4.04-6.99)	-1.08	-2.87 – 0.71	0.0007					

Results of PULSAR NCT04423718											
				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		
										assess non-inferiority in the primary endpoint: •Q12W is non-inferior to Q8W regarding the mean change in BCVA from baseline to Week 48 using a non-inferiority margin of 4 letters. •Q16W is non-inferior to Q8W regarding the mean change in BCVA from baseline to Week 48 using a non-inferiority margin of 4 letters. Mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate and treatment group (Q16W vs. Q8W and Q12W vs. Q8W), visit and the stratification variables (geographic region [Japan vs. Rest of World] and baseline BCVA [<60 vs. ≥60]) as fixed factors as well as terms for the interaction between baseline BCVA	

Results of PULSAR NCT04423718											
				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		
										and visit and for the interaction between treatment and visit. In line with the definition of estimands (see above), the primary analysis will be performed on the FAS and participants will be analyzed within their original randomized group (regardless of any changes to dose interval).	
Proportion of participants losing less than 15 letters in BCVA from baseline at Week 48	AFL 2mg q8w	336	321 (95.8%) (93.09-97.70 %)							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. Absolute numbers are not known	
	AFL 8mg q12w	335	316 (94.6%) (91.62-96.78 %)	-1.2%	-4.64-2.13 %		0.99	0.95 – 1.02			

Results of PULSAR NCT04423718											
				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 60	AFL 8mg q16w	338	319 (94.7%) (91.69-96.80 %)	-1.2 %	-4.57-2.16 %		0.99	0.96-1.02			
	AFL 2mg q8w	336	321 (95.8 %) (93.09-97.70 %)								
	AFL 8mg q12w	335	312 (93.4 %) (90.20-95.83%)	-2.4 %	-6.04-1.06 %		0.97	0.94-1.01			
Week 96	AFL 8mg q16w	338	320 (95.0 %) (92.05-97.03 %)	-0.9 %	-4.22-2.43%		0.99	0.96-1.02			
	AFL 2mg q8w	336	318 (94.9 %) (92.00-97.02%)								
	AFL 8mg q12w	335	308 (92.2 %) (88.80-94.85%)	-2.7 %	-6.62-1.05%		0.97	0.93-1.01			

Results of PULSAR NCT04423718											
				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**		
	AFL 8mg q16w	338	311 (92.3 %) (88.90-94.90%)	-2.6 %	-6.52-1.10%		0.97	0.93-1.01			
Change from baseline in National Eye Institute visual functioning questionnaire-25 – total score at week 48	AFL 2mg q8w	266	4.22 (2.85-5.59)							A mixed model for repeated measurements (MMRM) was used with baseline NEI-VFQ-25 total score as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. >=60]) as fixed factors, and terms for the interaction between baseline NEI-VFQ-25 total score and visit and the interaction between treatment and visit.	
	AFL 8mg q12w	285	3.50 (2.13-4.87)	-0.72	(-2.35 - 0.90)	0.3817					
	AFL 8mg q16w	266	3.35 (1.94-4.76)	-0.87	(-2.55 - 0.80)	0.3070					
Safety results										Proportion of participants with ocular treatment-emergent macular fibrosis summarized descriptively by treatment group in the safety analysis set population.	
Macular fibrosis											
Week 48	AFL 2mg q8w	336	4 (1.2%)								

Results of PULSAR NCT04423718											
				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		
			(0.33-3.02%)								
	AFL 8mg q12w	335	3 (0.9%)	-0.3%	-2.23-1.55%		0.75	0.17-3.34			
			(0.19-2.59%)								
	AFL 8mg q16w	338	3 (0.9%)	-0.3%	-2.24-1.53%		0.75	0.17-3.31			
			(0.18-2.57%)								
Week 60	AFL 2mg q8w	336	5 (1.5%)								
			(0.48-3.44%)								
	AFL 8mg q12w	335	3 (0.9%)	-0.6%	-2.65-1.29%		0.60	0.15-2.50			
			(0.19-2.59%)								
	AFL 8mg q16w	338	3 (0.9%)	-0.6%	-2.66-1.27%		0.60	0.14-2.48			
			(0.18-2.57%)								
Week 96	AFL 2mg q8w	336	5 (1.5 %)								
			(0.48-3.44%)								
	AFL 8mg q12w	335	4 (1.2 %)	-0.3%	-2.39-1.72%		0.80	0.22-2.96			

Results of PULSAR NCT04423718											
				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		
			(0.33-3.03%)								
	AFL 8mg q16w	338	3 (0.9 %)	-0.6%	-2.66-1.27%		0.60	0.14-2.48			
			(0.18-2.57%)								
TEAE increase in intraocular pressure related to intravitreal injection procedure										Proportion of participants with ocular treatment-emergent increase in intraocular pressure related to intravitreal injection procedure summarized descriptively by treatment group in the safety analysis set population.	
Week 48											
	AFL 2mg q8w	336	4 (1.2%)								
			(0.33-3.02%)								
	AFL 8mg q12w	335	5 (1.5%)	0.3%	-1.71-2.40%		1.25	0.34-4.63			
			(0.49-3.45%)								
	AFL 8mg q16w	338	5 (1.5%)	0.3%	-1.72-2.37%		1.24	0.34-4.59			
			(0.48-3.42%)								

Results of PULSAR NCT04423718											
				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 60											
	AFL 2mg q8w	336	7 (2.1%) (0.84-4.25%)								
	AFL 8mg q12w	335	5 (1.5%) (0.49-3.45%)	-0.6%	-2.93-1.62%		0.72	0.23-2.23			
	AFL 8mg q16w	338	6 (1.8%) (0.65-3.82%)	-0.3%	-2.68-2.00%		0.85	0.29-2.51			
Week 96	AFL 2mg q8w	336	4 (1.2%) 8 (2.4%) (1.03-4.64%)								
	AFL 8mg q12w	335	5 (1.5%) (0.49-3.45%)	-0.9%	-3.32-1.37%		0.63	0.21-1.90			
	AFL 8mg q16w	338	5 (1.5%) 8 (2.4%) (1.03-4.61%)	-0.0%	-2.55-2.51%		0.99	0.38-2.62			

Results of PULSAR NCT04423718											
				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 48	AFL 2mg q8w	336	2 (0.6%) (0.07-2.13%)								
	AFL 8mg q12w	335	4 (1.2%) (0.33-3.03%)	0.6%	-1.08-2.51%		2.01	0.37-10.88			
	AFL 8mg q16w	338	1 (0.3%) (0.01-1.64%)	-0.3%	-1.88-1.11%		0.50	0.05- 5.46			
Week 60	AFL 2mg q8w	336	4 (1.2%) (0.33-3.02%)								
	AFL 8mg q12w	335	4 (1.2%) (0.33-3.03%)	0.0%	-1.97-1.98%		1.00	0.25-3.98			

Results of PULSAR NCT04423718											
				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**		
	AFL 8mg q16w	338	1 (0.3%) (0.01-1.64%)	-0.9%	-2.76-0.58%		0.25	0.03-2.21			
Week 96	AFL 2mg q8w	336	7 (2.1%) (0.84-4.25%)								
	AFL 8mg q12w	335	6 (1.8%) (0.66-3.86%)	-0.3%	-2.67-2.03%		0.86	0.29-2.53			
	AFL 8mg q16w	338	3 (0.9%) (0.18-2.57%)	-1.2%	-3.46-0.75%		0.43	0.11-1.63			
Ocular TESAEs in study eye Week 48	AFL 2mg q8w	336	2 (0.6%) (0.07-2.13%)							Proportion of participants with ocular treatment-emergent serious adverse events summarized descriptively by treatment group in the safety analysis set population.	
	AFL 8mg q12w	335	6 (1.8%)	1.2%	-0.56-3.33%		3.01	0.61-14.80			

Results of PULSAR NCT04423718											
				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		
			(0.66-3.86%)								
	AFL 8mg q16w	338	5 (1.5%)	0.9%	-0.83-2.89%		2.49	0.49-12.72			
			(0.48-3.42%)								
Week 60	AFL 2mg q8w	336	4 (1.2%)								
			(0.33-3.02%)								
	AFL 8mg q12w	335	7 (2.1%)	0.9%	-1.19-3.21%		1.76	0.52-5.94			
			(0.84-4.26%)								
	AFL 8mg q16w	338	7 (2.1%)	0.9%	-1.21-3.17%		1.74	0.51- 5.89			
			(0.84-4.22%)								
Week 96	AFL 2mg q8w	336	4 (1.2 %)								
			(0.33-3.02%)								
	AFL 8mg q12w	335	10 (3.0 %)	1.8%	-0.42-4.36%		2.51	0.79-7.92			
			(1.44-5.42%)								
	AFL 8mg q16w	338	10 (3.0 %)	1.8%	-0.44-4.31%		2.49	0.79-7.85			

Results of PULSAR NCT04423718											
				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		
			(1.43-5.37%)								
Non-ocular TESAE										Proportion of participants with non-ocular treatment-emergent serious adverse events summarized descriptively by treatment group in the safety analysis set population.	
Week 48											
	AFL 2mg q8w	336	46 (13.7%)								
			(10.20-17.84%)								
	AFL 8mg q12w	335	34 (10.1%)	-3.5%	-8.53-1.39%		0.74	0.49-1.12			
			(7.13-13.89%)								
	AFL 8mg q16w	338	32 (9.5%)	-4.2%	-9.15-0.62%		0.69	0.45-1.06			
			(6.57-13.10%)								
Week 60											
	AFL 2mg q8w	336	53 (15.8%)								
			(12.04-20.12%)								
	AFL 8mg q12w	335	41 (12.2%)	-3.5%	-8.85-1.74%		0.78	0.53-1.13			

Results of PULSAR NCT04423718											
				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		
			(8.93-16.24%)								
	AFL 8mg q16w	338	41 (12.1%)	-3.6%	-8.94-1.61%		0.77	0.53-1.12			
Week 96			(8.85-16.09%)								
	AFL 2mg q8w	336	66 (19.6 %)								
			(15.53-24.30%)								
	AFL 8mg q12w	335	73 (21.8 %)	2.1%	-4.00-8.30%		1.11	0.82-1.49			
			(17.49-26.60%)								
	AFL 8mg q16w	338	64 (18.9 %)	-0.7	-6.70-5.27%		0.96	0.71-1.31			
			(14.90-23.53%)								

Appendix C. Comparative analysis of efficacy

[For meta-analyses, the table below can be used. For any type of comparative analysis (i.e. paired indirect comparison, network meta-analysis or MAIC analysis), describe the methodology and the results here in an appropriate format (text, tables and/or figures).]

Tabel 1 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: median overall survival		NA	NA	NA	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird).	Yes/No
Example: 1-year survival		10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird). The absolute difference was estimated by applying the	

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
								resulting HR to an assumed 1-year survival rate of 64.33% in the comparator group.	
Example: HRQoL		**−4.5**	−8.97 to −0.03	0.04	NA	NA	NA	HRQoL results for the studies included were synthesized using the standardized mean difference (SMD). The estimated meta-analytical SMD of −0.3 (95% CI −2.99 to −0.01) was transformed to the scale of ZZZ* assuming a population standard deviation of 15 on the ZZZ* scale. *Fill in the name of an appropriate measure of HRQoL.	
Insert outcome 4									

Appendix D. Literature searches for the clinical assessment

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

[Please refer to the treatment guideline for instructions as well as section 3 of the methods guide. Describe how the literature search was performed. Explain the selection of the search criteria and terms used, search filters, and the inclusion and exclusion criteria. Sufficient details should be provided so that the results may be reproduced.

If an existing/global systematic literature review (SLR) is (re)used, Appendix D must be filled out with data/information from such SLR and it must be clear how the SLR has been adapted to the current application. The inclusion and exclusion criteria, PRISMA flowchart, and list of excluded full text references should reflect the purpose of the application. Thus, unedited technical reports or SLRs will not be accepted as Appendix D. Please find an editable PRISMA flowchart at the end of this document.

Objective of the literature search: What questions is the literature search expected to answer?
Databases/other sources: Fill in the databases and other sources, e.g. conference material used in the literature search.]

Tabel 2 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	E.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm.yyyy
CENTRAL	Wiley platform		dd.mm.yyyy

Abbreviations:

Tabel 3 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
e.g. EMA website			dd.mm.yyyy

Abbreviations:

Tabel 4 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Manual search	List individual terms used to search in the conference material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

Abbreviations:

D.1.2 Search strategies

[Describe the development of the search strategy and search string. Specify the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time limits, etc.).]

[The search must be documented with exact search strings line by line as run, incl. results, for each database.]

Tabel 5 of search strategy table for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

D.1.3 Systematic selection of studies

[Describe the selection process, incl. number of reviewers and how conflicts were resolved. Provide a table with criteria for inclusion or exclusion.]

Tabel 6 Inclusion and exclusion criteria used for assessment of studies

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

[Insert the PRISMA flow diagram(s) here (see example here) or use the editable diagram at the end of this document.]

Tabel 7 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						
Study 2						

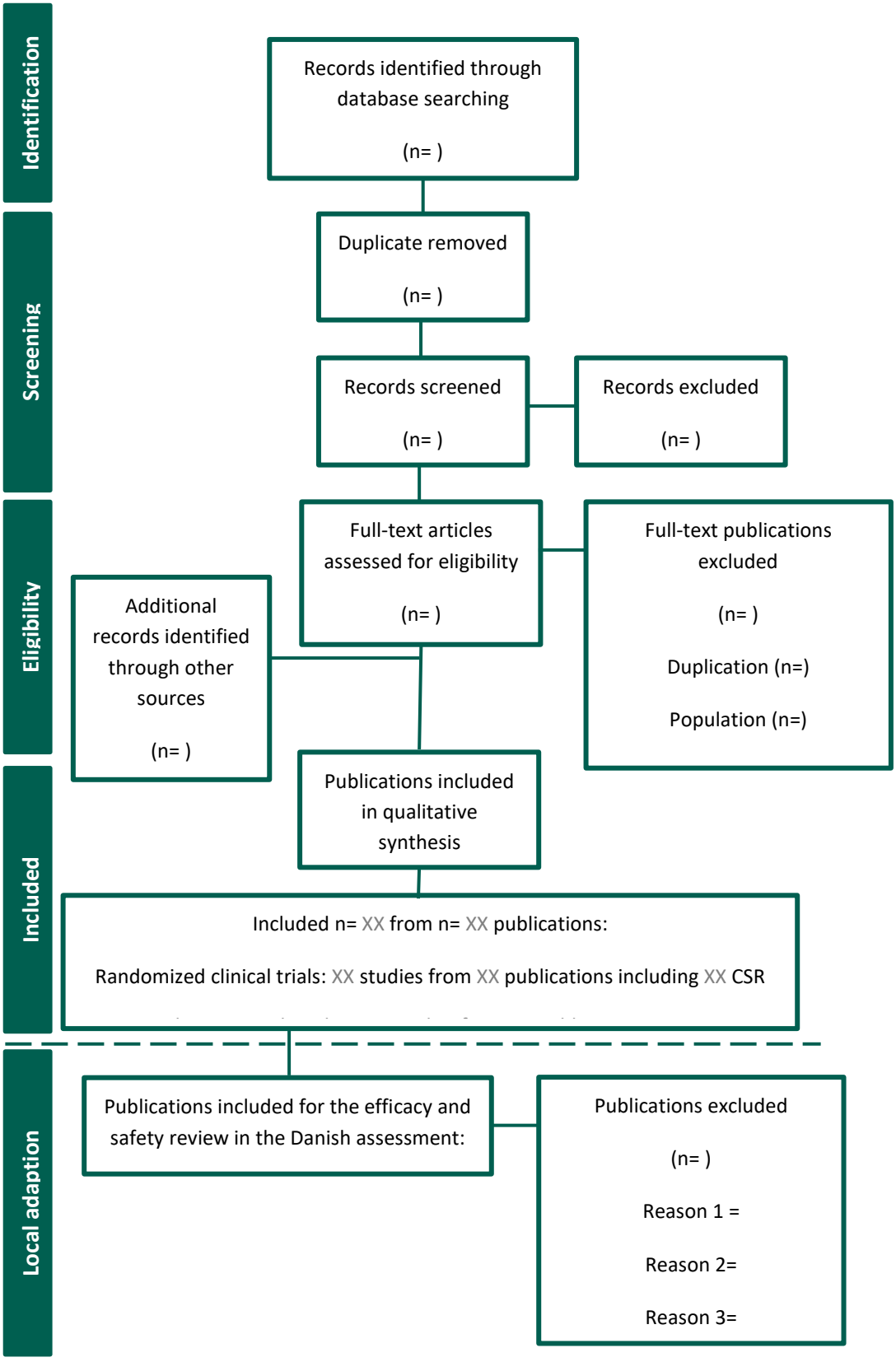
D.1.4 Quality assessment

[Describe strengths and weaknesses of the literature search performed.]

D.1.5 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted].

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



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