Medicinrådet

Bilag til direkte indplacering af aflibercept (8 mg dosering) i Medicinrådets behandlingsvejledning vedrørende lægemidler til diabetisk makulaødem (DME)

Vers. 1.0

Bilagsoversigt

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

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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 diabetisk makulaødem
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 veneokklusion (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	Pakningsstørrelse	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 diabetisk makulaødem”

Contact information

Contact information	
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Abbreviations

AE	adverse event
AMD	age-related macular degeneration
BCVA	best corrected visual acuity
BRB	blood-retina barrier
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRT	central retinal thickness
CSDME	clinically significant diabetic macular oedema
CSME	clinically significant macular oedema
DME	diabetic macular oedema
DR	diabetic retinopathy
DRCR.net	Diabetic Retinopathy Clinical Research Network
DRM	dose regimen modification
DRSS	Diabetic Retinopathy Severity Scale
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAS	full analysis set
G-SAP	global statistical analysis plan
HAS	Haute Autorité de Santé
HR	hazard ratio
IOP	intraocular pressure
IRF	intraretinal fluid
logMAR	logarithm of the minimum angle of resolution
LS	least square
MLP	macular laser photocoagulation
MMRM	Mixed Models for Repeated Measures
nAMD	neovascular age-related macular degeneration
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire-25
NPDR	non-proliferative diabetic retinopathy
NR	not reported
OCT	optical coherence tomography
PDR	proliferative diabetic retinopathy

PlGF	placental growth factor
PPS	per protocol set
PTI	personalized treatment interval
SAF	safety analysis set
SAP	statistical analysis plan
SD-OCT	spectral-domain optical coherence tomography
SRF	subretinal fluid
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
VA	visual acuity
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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	Impaired vision due to macular oedema caused by diabetes
Marketing authorization holder in Denmark	Bayer A/S
ATC code	S01LA05
Combination therapy and/or co-medication	None
(Expected) Date of EC approval	3-15 January 2014
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Neovascular age related macula degeneration - nAMD
Other indications that have been evaluated by the DMC (yes/no)	Ongoing evaluation of neovascular AMD
Dispensing group	NA
Packaging – types, sizes/number of units and concentrations	Package with a single vial of 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 visual impairment due to diabetic macular oedema (DME)
Dosage regiment and administration:	Intravitreal injection of aflibercept 8 mg (0.07 ml) administered Q12W after the 3 initial injections at 4-week interval Intravitreal injection of aflibercept 8 mg (0.07 ml) administered Q16W after the 3 initial injections at 4-week interval
Choice of comparator [if any]	Intravitreal injection of aflibercept 2 mg (0.05 ml) administered Q8W after the 5 initial injections at 4-week interval
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 in 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 ○ The primary analysis endpoint was met as the treatment with aflibercept 8 mg every 12 and 16 weeks demonstrated non-inferiority to aflibercept 2 mg using the margin of 4 letters, with the least square (LS) mean changes in BCVA from baseline to week 48 of 8.10 letters, 7.23 letters, and 8.67 letters for aflibercept 8 mg Q12W, aflibercept 8 mg Q16W, and aflibercept 2 mg, respectively At week 48, 60 and 96, the proportion of patient losing ≥15 ETDRS letters were comparable between the 3 different 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 similar improvements in central retinal thickness (CRT), compared with aflibercept 2 mg dosed every 8 weeks. At week 48, aflibercept 8 mg administered in two extended dosing regimens (every 12 and 16 weeks) demonstrated a comparable efficacy with aflibercept 2 mg in terms of improvement in the vision-related quality of life as measured by the mean improvement in the NEI-VFQ-25 total score.

Summary	
Most important serious adverse events for the intervention and comparator	The safety of aflibercept 8 mg administered in 2 extended-dosing regimens (every 12 and 16 weeks) in the PHOTON 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 proportions of patients with any ocular treatment-emergent adverse event (TEAE) through week 60 were similar across all 3 treatment groups (44.8% for aflibercept 8 mg Q12W, 44.8% for aflibercept 8 mg Q16W, and 43.7% for aflibercept 2 mg Q8W). ○ The proportion of participants with ocular treatment-emergent serious adverse events (SAEs) in the study eye was very low, and only 5 of these SAEs were reported in 4 patients through week 60 ○ The rates of intraocular inflammation were 1.2% for aflibercept 8 mg Q12W and 0.6% for aflibercept 8 mg Q16W compared with 0.6% for aflibercept 2 mg through week 60. None of the events were serious ○ There were no clinically relevant differences in the intraocular pressure between the treatment groups through week 60 ○ In the aflibercept 8 mg groups, there were no cases of endophthalmitis and no new safety signals through week 60

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 diabetisk makulaødem".

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 (1, 2) (Eylea® 8 mg SmPC). Because of its much higher binding affinity than the native receptors, aflibercept binds to these proteins more tightly than either ranibizumab, bevacizumab, or brolucizumab (2,3).

Aflibercept 2 mg is a widely established and effective first-line treatment option for DME, which is broadly used in clinical practice and recommended in clinical guidelines (4,5,6,7). 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 the treatment efficacy and patient safety while reducing the treatment burden and need for healthcare resources. Furthermore, the improved treatment durability and reduced treatment burden are 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 (1) (Eylea® 8 mg SmPC). VEGF and PlGF have been implicated in the early and late pathogenesis of the disease progress in DR and DME (8, 9). VEGF acts via 2 receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells (1) (Eylea® 8 mg SmPC). PlGF binds only to VEGFR-1, which is also present on the surface of leukocytes (1). Excessive activation of these receptors by VEGF-A can result in excessive vascular permeability and pathological angiogenesis (4, 1). PlGF can synergise with VEGF-A in these processes and is also known to promote leukocyte infiltration and vascular inflammation (1) (Eylea® 8 mg SmPC).

Overview of intervention	
Therapeutic indication relevant for the assessment	Aflibercept 8 mg is indicated in adults for the treatment of visual impairment due to diabetic macular oedema (DME)
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	Aflibercept 8 mg treatment is initiated with 1 injection per month for 3 consecutive doses. Injection intervals may then be extended up to every 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

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 DME.

[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
PHOTON NCT04429503 Not published in scientific journal	A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study	The ongoing masked part of the study (up to week 96) consists of a 3-week screening/baseline period, a 92-week treatment period, and an end-of-study visit at week 96. The optional open-label extension phase will include an additional 60 weeks of treatment with aflibercept 8 mg, with an end-of-study visit at week 156	Start: 29/06/20 Primary completion: 30/05/22 Study completion: 29/06/24	Patients with central involvement of diabetic macula edema	Intravitreal injection of aflibercept 8 mg administered every 12 weeks (Q12W), after 3 initial injections at 4-week intervals Intravitreal injection of aflibercept 8 mg administered every 16 weeks (Q16W), after 3 initial injections at 4-week intervals	Intravitreal injection of aflibercept 2 mg 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 in 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 similar improvements in central retinal thickness (CRT), compared with aflibercept 2 mg dosed every 8 weeks. At week 48, aflibercept 8 mg administered in two extended dosing regimens (every 12 and 16 weeks) demonstrated a comparable efficacy with aflibercept 2 mg in terms of improvement in the vision-related quality of life as measured by the mean improvement in the NEI-VFQ-25 total score.

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
								At week 48, 60 and 96, the safety of aflibercept 8 mg administered in 2 extended-dosing regimens (every 12 and 16 weeks) in the PHOTON 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 adverse 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 diabetic macular edema?

5.1 Efficacy of afIlibercept 8 mg compared to aflibercept 2 mg for patients with DME

5.1.1 Relevant studies

Overview of the pivotal phase 3 PHOTON study for aflibercept 8 mg in diabetic macular oedema

PHOTON is an ongoing phase 2/3, multicentre, randomised, double-masked study in participants with DME involving the centre of the macula that investigates the efficacy, safety, and tolerability of intravitreal administration of aflibercept 8 mg compared with aflibercept 2 mg. This document describes the results of the pre-planned primary analysis at week 48 and data from the last cut-off at week 60. The document will be updated upon the availability of data from later data cuts.

The primary objective of the study is 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 a non-inferior BCVA change compared with aflibercept 2 mg every 8 weeks (after 5 initial injections at 4-week intervals) in participants with DME. The secondary objectives are to determine the effect of aflibercept 8 mg versus aflibercept 2 mg on anatomic and other visual measures of response, 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/baseline period, a 92-week treatment period, and an end-of-study visit at week 96. The optional open-label extension phase will include an additional 60 weeks of treatment with aflibercept 8 mg, with an end-of-study visit at week 156, for which exploratory analyses will be reported separately.

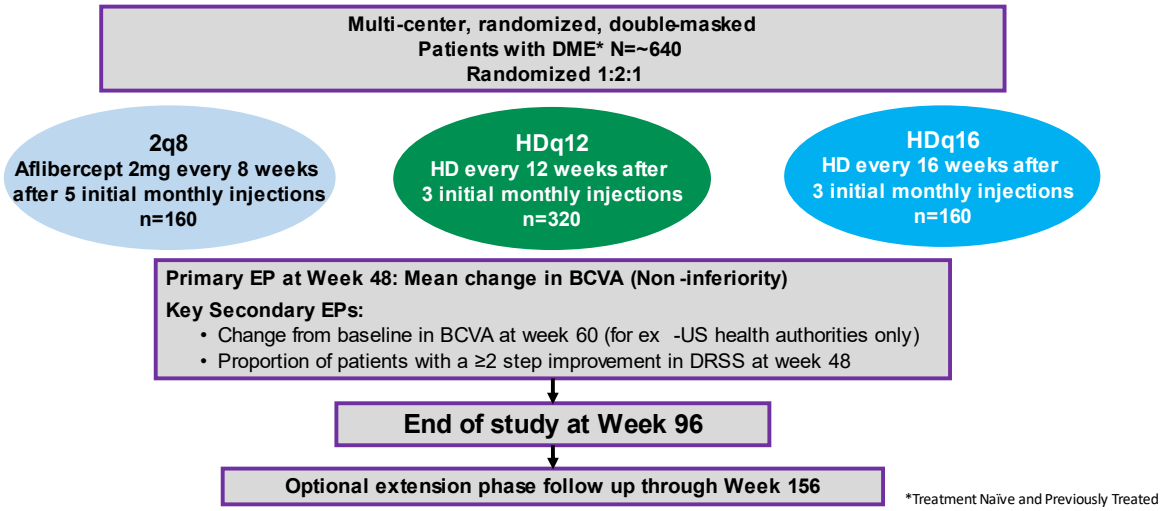
The study is being conducted at 138 centres in Canada, Czech Republic, Germany, Hungary, Japan, the United Kingdom, and the United States.

Participants were randomly assigned in a 1:2:1 ratio to 1 of 3 parallel treatment groups:

- Aflibercept 2 mg administered Q8W and at 4-week intervals after the 5 initial injections as indicated in the label (100)
- Aflibercept 8 mg administered Q12W and at 4-week intervals after the 3 initial injections

- Aflibercept 8 mg administered Q16W and at 4-week intervals after the 3 initial injections

Figure 1 PHOTON study design overview



2q8=aflibercept 2 mg every 8 weeks (Q8W); BCVA=best corrected visual acuity; DME=diabetic macular oedema; DRSS=Diabetic Retinopathy Severity Scale; EP=endpoint; HD=high dose, i.e., aflibercept 8 mg; N=total number of participants; n=number of participants per group; q12=every 12 weeks (Q12W); q16=every 16 weeks (Q16W); US=United States.

Source: PHOTON Clinical Study Protocol.

5.1.2 Comparability of studies

Not relevant for this 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 DME.

Table 2 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety. PHOTON study: Demographics and baseline disease characteristics

	Aflibercept 2 mg Q8W	Aflibercept 8 mg		
		Q12W	Q16W	Pooled
Age (years)				
Mean (SD)	63.0 (9.78)	62.1 (11.13)	61.9 (9.50)	62.0 (10.61)
Median	64.0	63.0	62.0	63.0
Min : Max	38 : 90	24 : 87	37 : 83	24 : 87
Age category, n (%)				
<55 years	29 (17.4%)	77 (23.5%)	38 (23.3%)	115 (23.4%)
≥55 to <65 years	63 (37.7%)	108 (32.9%)	54 (33.1%)	162 (33.0%)

	Aflibercept 2 mg Q8W	Aflibercept 8 mg		
		Q12W	Q16W	Pooled
≥65 to <75 years	54 (32.3%)	107 (32.6%)	57 (35.0%)	164 (33.4%)
≥75 years	21 (12.6%)	36 (11.0%)	14 (8.6%)	50 (10.2%)
Ethnicity, n (%)				
Hispanic or Latino	31 (18.6%)	54 (16.5%)	34 (20.9%)	88 (17.9%)
Not Hispanic or Latino	133 (79.6%)	266 (81.1%)	126 (77.3%)	392 (79.8%)
Not reported	3 (1.8%)	8 (2.4%)	3 (1.8%)	11 (2.2%)
Race, n (%)				
American Indian or Alaska Native	0	2 (0.6%)	0	2 (0.4%)
Asian	30 (18.0%)	48 (14.6%)	23 (14.1%)	71 (14.5%)
Black or African American	18 (10.8%)	35 (10.7%)	9 (5.5%)	44 (9.0%)
Native Hawaiian or Other Pacific Islander	0	1 (0.3%)	0	1 (0.2%)
White	112 (67.1%)	231 (70.4%)	128 (78.5%)	359 (73.1%)
Other	0	1 (0.3%)	0	1 (0.2%)
Not reported	4 (2.4%)	6 (1.8%)	1 (0.6%)	7 (1.4%)
Sex, n (%)				
Female	75 (44.9%)	118 (36.0%)	64 (39.3%)	182 (37.1%)
Male	92 (55.1%)	210 (64.0%)	99 (60.7%)	309 (62.9%)
Geographical region, n (%)				
Japan	20 (12.0%)	37 (11.3%)	17 (10.4%)	54 (11.0%)
Rest of World	147 (88.0%)	291 (88.7%)	146 (89.6%)	437 (89.0%)
Body mass index (kg/m^2)				
Mean (SD)	29.91 (6.525)	30.44 (6.156)	31.02 (6.123)	30.63 (6.145)
Median	28.70	29.40	30.00	29.65
Min : Max	17.7 : 48.6	17.7 : 52.1	20.1 : 58.5	17.7 : 58.5
Systolic blood pressure (mm Hg)				
Mean (SD)	135.92 (14.792)	134.06 (14.627)	133.47 (13.766)	133.86 (14.335)
Median	137.00	134.00	133.50	134.00
Min : Max	97.0 : 167.0	98.5 : 170.0	102.0 : 167.0	98.5 : 170.0
Diastolic blood pressure (mm Hg)				
Mean (SD)	75.35 (8.928)	75.21 (9.445)	75.29 (9.216)	75.24 (9.361)
Median	76.00	75.50	75.50	75.50
Min : Max	47.5 : 91.5	46.5 : 108.5	50.5 : 95.5	46.5 : 108.5
Haemoglobin A1c at baseline (%)				
Mean (SD)	8.14 (1.482)	7.94 (1.546)	7.84 (1.502)	7.91 (1.531)
Median	7.90	7.60	7.60	7.60
Min : Max	5.5 : 13.6	5.1 : 13.6	4.5 : 12.0	4.5 : 13.6

	Aflibercept 2 mg Q8W	Aflibercept 8 mg		
		Q12W	Q16W	Pooled
Haemoglobin A1c at baseline category, n (%)				
≤8%	90 (53.9%)	193 (58.8%)	106 (65.0%)	299 (60.9%)
>8%	76 (45.5%)	133 (40.5%)	55 (33.7%)	188 (38.3%)
Missing	1	2	2	4
History of renal impairment, n (%)				
Normal	111 (66.5%)	217 (66.2%)	112 (68.7%)	329 (67.0%)
Mild	38 (22.8%)	72 (22.0%)	38 (23.3%)	110 (22.4%)
Moderate	13 (7.8%)	22 (6.7%)	8 (4.9%)	30 (6.1%)
Severe	4 (2.4%)	11 (3.4%)	5 (3.1%)	16 (3.3%)
Missing	1	6	0	6
History of hepatic impairment, n (%)				
Yes	4 (2.4%)	12 (3.7%)	4 (2.5%)	16 (3.3%)
No	163 (97.6%)	316 (96.3%)	159 (97.5%)	475 (96.7%)
History of cerebrovascular disease, n (%)				
Yes	19 (11.4%)	21 (6.4%)	10 (6.1%)	31 (6.3%)
No	148 (88.6%)	307 (93.6%)	153 (93.9%)	460 (93.7%)
History of ischaemic heart disease, n (%)				
Yes	28 (16.8%)	64 (19.5%)	22 (13.5%)	86 (17.5%)
No	139 (83.2%)	264 (80.5%)	141 (86.5%)	405 (82.5%)
Duration of diabetes (years)				
Mean (SD)	15.9 (10.04)	15.1 (9.96)	15.7 (10.67)	15.3 (10.20)
Median	15.2	14.0	14.4	14.2
Min : Max	1 : 61	0 : 51	0 : 54	0 : 54
Diabetes type, n (%)				
Type I	11 (6.6%)	18 (5.5%)	9 (5.5%)	27 (5.5%)
Type II	156 (93.4%)	310 (94.5%)	154 (94.5%)	464 (94.5%)
Insulin-dependent	84 (50.3%)	150 (45.7%)	85 (52.1%)	235 (47.9%)
Non–insulin dependent	73 (43.7%)	160 (48.8%)	68 (41.7%)	228 (46.4%)
NEI-VFQ-25 total score at baseline				
Mean (SD)	76.65 (15.889)	76.79 (17.316)	77.86 (15.578)	77.15 (16.751)
Median	79.62	81.41	80.79	81.40
Min : Max	29.2 : 98.2	15.1 : 100.0	18.6 : 99.4	15.1 : 100.0

Max=maximum; Min=minimum; n=number; NEI-VFQ-25=National Eye Institute Visual Function Questionnaire-25; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; SD=standard deviation.

Source: PHOTON Clinical Study Report (week 60)

PHOTON study: baseline disease characteristics of the study eye

	Aflibercept 2 mg Q8W	Aflibercept 8 mg		
		Q12W	Q16W	Pooled
BCVA (ETDRS letter score)				
n	167	328	163	491
Mean (SD)	61.5 (11.22)	63.6 (10.10)	61.4 (11.76)	62.9 (10.72)
Median	63.0	65.0	64.0	65.0
Q1 : Q3	54.0 : 70.0	57.0 : 72.0	55.0 : 71.0	56.0 : 71.0
Min : Max	24 : 78	27 : 79	29 : 78	27 : 79
Baseline BCVA category				
≤73 letters	147 (88.0%)	269 (82.0%)	140 (85.9%)	409 (83.3%)
>73 letters	20 (12.0%)	59 (18.0%)	23 (14.1%)	82 (16.7%)
CRT (microns)				
N	167	327	163	490
Mean (SD)	457.2 (144.00)	449.1 (127.39)	460.3 (117.84)	452.9 (124.29)
Median	417.0	431.0	432.0	431.0
Q1 : Q3	346.0 : 532.0	359.0 : 518.0	371.0 : 540.0	362.0 : 526.0
Min : Max	260 : 1014	229 : 1309	255 : 926	229 : 1309
Missing	0	1	0	1
CRT category per reading centre[a]				
<400 microns	72 (43.1%)	134 (40.9%)	65 (39.9%)	199 (40.5%)
≥400 microns	95 (56.9%)	194 (59.1%)	98 (60.1%)	292 (59.5%)
CRT category per IWRS (used for stratification)[b]				
<400 microns	69 (41.3%)	138 (42.1%)	69 (42.3%)	207 (42.2%)
≥400 microns	98 (58.7%)	190 (57.9%)	94 (57.7%)	284 (57.8%)
IOP (mm Hg)				
n	167	328	163	491
Mean (SD)	15.9 (2.99)	15.3 (3.24)	14.9 (3.25)	15.2 (3.25)
Median	16.0	15.0	15.0	15.0
Q1 : Q3	14.0 : 18.0	13.0 : 18.0	13.0 : 17.0	13.0 : 17.0
Min : Max	8 : 23	8 : 24	7 : 24	7 : 24
DRSS				
10	0	1 (0.3%)	2 (1.2%)	3 (0.6%)
12	0	2 (0.6%)	0	2 (0.4%)
14	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
15	1 (0.6%)	0	0	0
20	3 (1.8%)	13 (4.0%)	2 (1.2%)	15 (3.1%)
35	66 (39.5%)	121 (36.9%)	66 (40.5%)	187 (38.1%)

	Aflibercept 2 mg Q8W	Aflibercept 8 mg		
		Q12W	Q16W	Pooled
43	34 (20.4%)	59 (18.0%)	36 (22.1%)	95 (19.3%)
47	17 (10.2%)	46 (14.0%)	15 (9.2%)	61 (12.4%)
53	22 (13.2%)	34 (10.4%)	11 (6.7%)	45 (9.2%)
61	9 (5.4%)	20 (6.1%)	9 (5.5%)	29 (5.9%)
65	4 (2.4%)	11 (3.4%)	9 (5.5%)	20 (4.1%)
71	1 (0.6%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
75	0	1 (0.3%)	0	1 (0.2%)
90 (non-gradable)	9 (5.4%)	18 (5.5%)	10 (6.1%)	28 (5.7%)
Prior DME treatment per EDC, n (%)[c]				
Yes	74 (44.3%)	143 (43.6%)	71 (43.6%)	214 (43.6%)
No	93 (55.7%)	185 (56.4%)	92 (56.4%)	277 (56.4%)
Prior DME treatment per IWRS (used for stratification), n (%)[d]				
Yes	76 (45.5%)	149 (45.4%)	72 (44.2%)	221 (45.0%)
No	91 (54.5%)	179 (54.6%)	91 (55.8%)	270 (55.0%)

BCVA=best corrected visual acuity; CRT=central retinal thickness; DME=diabetic macular oedema; DRSS=Diabetic Retinopathy Severity Score; EDC=electronic data capture; ETDRS=Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; IWRS=interactive web response system; Max=maximum; Min=minimum; n=number; Q1=quartile 1; Q3=quartile 3; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; SD=standard deviation.

[a]Baseline values; used for subgroup analyses.

[b]Reflects the site entry of reading centre values from the screening visit into IWRS; 10 patients were stratified incorrectly, based on incorrect data entry in the IWRS.

[c]Used for week 48 subgroup analyses. However, before the week 60 database lock, the prior DME treatment status was changed from *No* to *Yes* for 2 participants in the Q12W group; the updated status was used for week 60 analyses.

[d]Reflects entry of prior DME treatment information by site into IWRS; 47 patients had data entered inconsistently between IWRS and EDC.

Source: PHOTON Clinical Study Report (week 60).

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

PHOTON study: Patient disposition

The disposition of patients in PHOTON is described in Table 3. A total of 970 patients were screened; 310 of them failed to meet the inclusion/exclusion criteria, which was the most frequent reason for failure at the screening. Overall, 660 patients were randomised, and 658 patients were treated (FAS and SAF populations). Of these, 613 patients completed the study treatment phase through week 48 and 596 patients through week 60.

Table 3 PHOTON study: Patient disposition through week 60

	Aflibercept 2 mg Q8W (N=167)	Aflibercept 8 mg			Total (N=660)
		Q12W (N=329)	Q16W (N=164)	Pooled (N=493)	
Week 48					
Number of patients who completed week 48	157 (94.0%)	300 (91.2%)	156 (95.1%)	456 (92.5%)	613 (92.9%)
Number of patients who discontinued prior to week 48	10 (6.0%)	29 (8.8%)	8 (4.9%)	37 (7.5%)	47 (7.1%)
Reasons for discontinuation prior to week 48					
Noncompliance with protocol by the subject	1 (0.6%)	0	0	0	1 (0.2%)
Adverse event	0	4 (1.2%)	1 (0.6%)	5 (1.0%)	5 (0.8%)
Decision by the investigator/sponsor	0	4 (1.2%)	1 (0.6%)	5 (1.0%)	5 (0.8%)
Withdrawal of consent by subject	4 (2.4%)	7 (2.1%)	2 (1.2%)	9 (1.8%)	13 (2.0%)
Lost to follow-up	1 (0.6%)	5 (1.5%)	1 (0.6%)	6 (1.2%)	7 (1.1%)
Death	4 (2.4%)	9 (2.7%)	3 (1.8%)	12 (2.4%)	16 (2.4%)
Due to COVID-19	0	0	0	0	0
Week 60					
Number of patients who completed week 60	155 (92.8%)	289 (87.8%)	152 (92.7%)	441 (89.5%)	596 (90.3%)
Number of patients who discontinued prior to week 60	12 (7.2%)	40 (12.2%)	12 (7.3%)	52 (10.5%)	64 (9.7%)
Reasons for discontinuation prior to week 60					
Noncompliance with protocol by the subject	1 (0.6%)	1 (0.3%)	0	1 (0.2%)	2 (0.3%)
Adverse event	0	4 (1.2%)	2 (1.2%)	6 (1.2%)	6 (0.9%)
Decision by the investigator/sponsor	0	6 (1.8%)	2 (1.2%)	8 (1.6%)	8 (1.2%)
Withdrawal of consent by subject	4 (2.4%)	12 (3.6%)	2 (1.2%)	14 (2.8%)	18 (2.7%)
Lost to follow-up	2 (1.2%)	8 (2.4%)	2 (1.2%)	10 (2.0%)	12 (1.8%)
Death	5 (3.0%)	9 (2.7%)	4 (2.4%)	13 (2.6%)	18 (2.7%)
Due to COVID-19	0	0	0	0	0

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

Source: PHOTON Clinical Study Report (week 60).

Clinical efficacy results from the PHOTON study: 48-week results

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 PHOTON study found that aflibercept 8 mg administered Q12W or Q16W was non-inferior to aflibercept 2 mg Q8W in terms of LS mean improvement from BCVA as measured by the ETDRS letter score at week 48 (Table 4). The primary analysis of the change from baseline in BCVA resulted in LS mean changes from baseline to week 48 (**0**) of 8.67 letters for aflibercept 2 mg Q8W compared with 8.10 letters for aflibercept 8 mg Q12W (p value for non-inferiority was <0.0001) and 7.23 letters for aflibercept 8 mg Q16W (p value for non-inferiority versus aflibercept 2 mg Q8W was 0.0031).

The results of the 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 PHOTON Clinical Study Report (week 60).

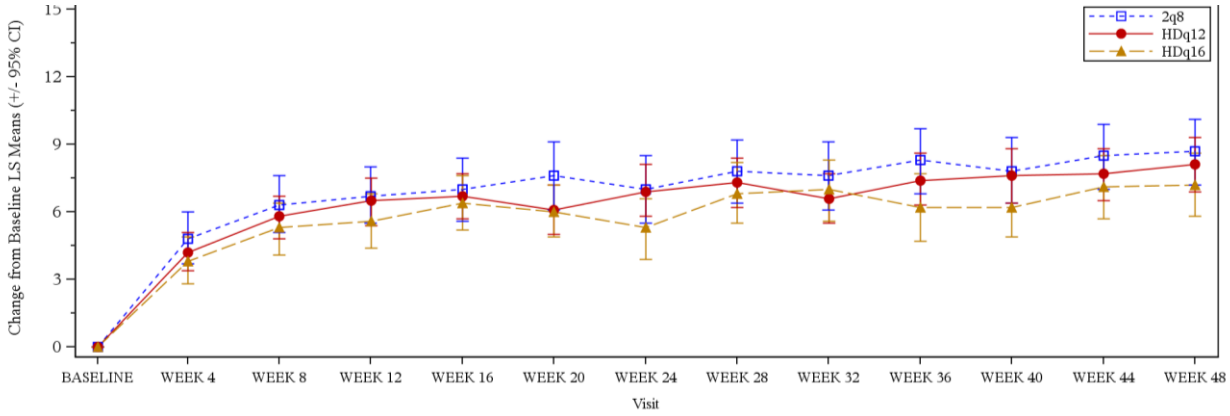
Table 4 Change from baseline in BCVA measured by the ETDRS letter score at week 48

	Aflibercept 2 mg	Aflibercept 8 mg	
	Q8W	Q12W	Q16W
Full analysis set	N=167	N=328	N=163
Number of patients with week 48 data	150	277	149
Baseline mean	61.47	63.63	61.44
Mean (SD) change from baseline	9.21 (8.99)	8.77 (8.95)	7.86 (8.38)
LS mean (SE) change from baseline	8.67 (0.73)	8.10 (0.61)	7.23 (0.71)
p value of 1-sided test for non-inferiority vs aflibercept 2 mg Q8W at a margin of 4 letters	-	<0.0001	0.0031
Difference in LS mean vs aflibercept 2 mg Q8W (95% CI)	-	-0.57 (-2.26, 1.13)	-1.44 (-3.27, 0.39)

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; ETDRS=Early Treatment Diabetic Retinopathy Study; LS=least square; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; SD=standard deviation; SE=standard error.

Source: PHOTON Clinical Study Report (week 60).

Figure 2 Least squares mean change from baseline in BCVA (Full analysis set)



2q8=aflibercept 2 mg every 8 weeks (Q8W); BCVA=best corrected visual acuity; CI=confidence interval; CRT=central retinal thickness; HD=high dose, i.e., aflibercept 8 mg; LS=least square; MMRM=Mixed Models for Repeated Measures; q12=every 12 weeks (Q12W); q16=every 16 weeks (Q16W).

Source: PHOTON 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

Few patients (from 0.6% up to 2.1%) lost 15 or more letters through week 48 regardless of the treatment group.

Table 5 Clinical efficacy from the PHOTON study: 48-week exploratory endpoints

Exploratory endpoints through week 48, Full analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg *(p value versus aflibercept 2 mg Q8W)* Q12W N=328	*p value*[a]	Q16W N=163	*p value*[a]
Proportion of patients who	N=165	N=326		N=163	
▪ Gained ≥10 letters in BCVA	49.1%	40.5%	*NR*	35.0%	*NR*
▪ Gained ≥5 letters in BCVA	68.5%	70.9%	*NR*	65.6%	*NR*
▪ Lost ≥15 letters in BCVA	1.2%	2.1%	*NR*	0.6%	*NR*
▪ Lost ≥10 letters in BCVA	1.2%	3.4%	*NR*	1.2%	*NR*
▪ Lost ≥5 letters in BCVA	3.0%	6.4%	*NR*	6.1%	*NR*

BCVA=best corrected visual acuity; CMH=Cochran-Mantel-Haenszel; NR=not reported; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; SRF=subretinal fluid.

[a]Nominal p value for the 2-sided CMH superiority test.

Source: PHOTON Clinical Study Report (week 60).

Change from baseline in central retinal thickness at week 48 for aflibercept 8 mg (Q12W and Q16W) were non-inferior to aflibercept 2 mg

The PHOTON study showed robust reductions from baseline in CRT at week 48 across all treatment groups. The LS mean changes from baseline in CRT at week 48 in the aflibercept 8 mg Q12W and Q16W treatment groups were similar to the aflibercept 2 mg Q8W group. The LS mean change in CRT was -176.77 in the aflibercept 8 mg Q12W group, -148.84 in the aflibercept 8 mg Q16W group, and -164.85 in the aflibercept 2 mg Q8W group (Table 6).

The LS mean changes (Table 6) in CRT over time were similar across all 3 aflibercept groups, and minor numerical differences were not considered clinically relevant. Although reductions from baseline in CRT were consistently observed at all timepoints, some fluctuation in mean CRT was seen in all treatment groups with attenuation in magnitude over the course of 48 weeks.

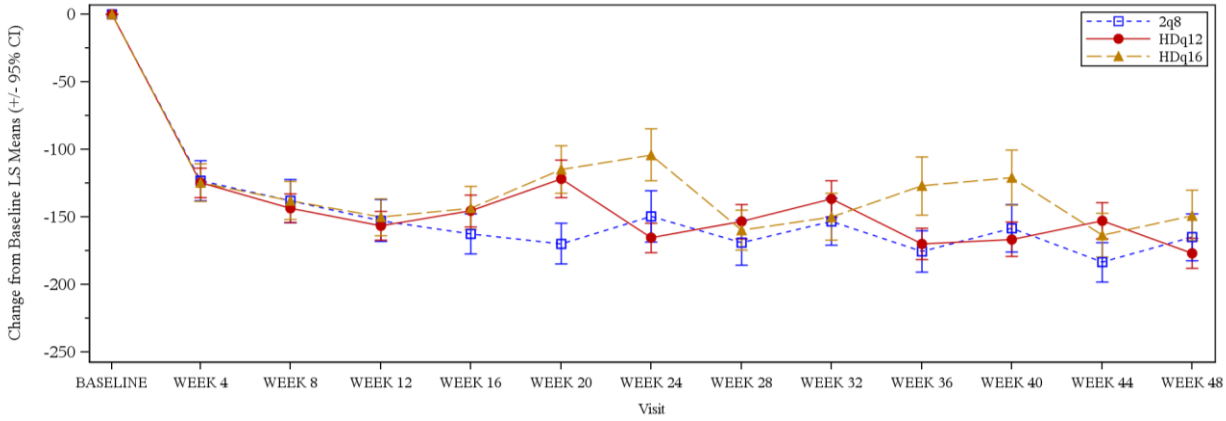
Table 6 Change from baseline in CRT at week 48

Full analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163
Number of patients with week 48 data	148	276	149
LS mean (SE) change from baseline	-164.85 (8.79)	-176.77 (5.73)	-148.84 (9.45)
Mean (SD) change from baseline	-165.31 (140.22)	-171.65 (141.52)	-148.30 (133.20)
Baseline mean	457.25	449.15	460.32
Adjusted difference % versus aflibercept 2 mg Q8W (2-sided 95% CI)	-	-11.92 (-30.30, 6.47)	16.01 (-7.53, 39.54)
p value	-	0.2028	0.1817

CI=confidence interval; CRT=central retinal thickness; LS=least square; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; SD=standard deviation; SE=standard error.

Source: PHOTON Clinical Study Report (week 60).

Figure 3 Least square mean change from baseline in CRT by visit through week 48, observed cases (full analysis set)



2q8=aflibercept 2 mg every 8 weeks (Q8W); CI=confidence interval; CRT=central retinal thickness; FAS=full analysis set; HD=high dose, i.e., aflibercept 8 mg; LS=least square; q12=every 12 weeks (Q12W); q16=every 16 weeks (Q16W).

Source: PHOTON Clinical Study Report (week 48).

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 PHOTON study showed that aflibercept 8 mg Q12W and Q16W treatments provided a comparable efficacy to aflibercept 2 mg Q8W in terms of an improvement in the vision-related quality of life as measured by the NEI-VFQ-25 total score at week 48. The LS mean change from baseline in the NEI-VFQ-25 total score at week 48 was 4.06 in the aflibercept 8 mg Q12W group and 2.94 in the aflibercept 8 mg Q16W group, compared with 2.82 in the aflibercept 2 mg Q8W group (Table 7).

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

	Aflibercept 2 mg	Aflibercept 8 mg	
	Q8W	Q12W	Q16W
Full analysis set	N=167	N=328	N=163
Number of patients with week 48 data	150	276	149
LS mean (SE) change from baseline	2.82 (1.10)	4.06 (0.80)	2.94 (0.93)
Mean (SD) change from baseline	4.41 (13.84)	5.64 (12.56)	4.16 (10.94)
Baseline mean	76.65	76.79	77.86
Adjusted difference % versus aflibercept 2 mg Q8W (2-sided 95% CI)	-	1.25 (-1.09, 3.58)	0.13 (-2.37, 2.62)
p value	-	0.2941	0.9208

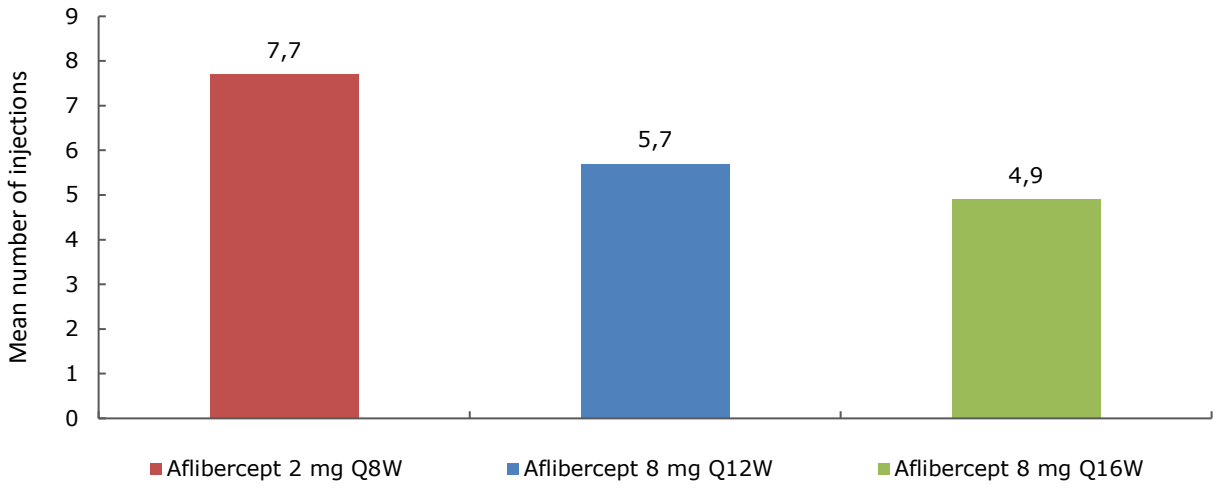
CI=confidence interval; LS=least square; NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; SD=standard deviation; SE=standard error.

Source: PHOTON 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 patients treated with aflibercept 2 mg. The mean number of injections over 48 weeks was 5.7 in the aflibercept 8 mg Q12W group, 4.9 in the aflibercept 8 mg Q16W group, and 7.7 in the aflibercept 2 mg Q8W group (Figure 4

Figure 4 Mean number of aflibercept injections through week 48



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

Source: PHOTON 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 patients maintained with Q16W treatment interval through week 48 in the Q16W group

The majority of patients in the aflibercept 8 mg Q16W group (89.1%) were maintained on the assigned dosing interval through week 48 (Table 8).

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

The majority of patients in the aflibercept 8 mg Q12W group (91.0%) and Q16W group (96.2%) were maintained on the Q12W or longer dosing interval through week 48. In the pooled aflibercept 8 mg group, substantial majority (92.8%) of patients were maintained on the Q12W or longer dosing interval through week 48 (Table 8).

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

The proportion of patients with Q12W or longer treatment interval as the last treatment interval at week 48 was 87.3% in the aflibercept 8 mg Q12W group and 93.6% in the Q16W group, and 89.5% in the pooled aflibercept 8 mg group. The proportion of patients with Q16W or longer treatment interval as the last treatment interval at week 48 was 87.2% in the aflibercept 8 mg Q16W group (Table 8).

Table 8 Summary of treatment exposure in the study eye through week 48

		Aflibercept 8 mg		
Assessment at the last injection visit[a]	Aflibercept 2 mg Q8W N=157	Q12W N=300	Q16W N=156	Pooled N=456
Patients maintained with Q12W or longer dosing interval	-	273 (91.0%)	150 (96.2%)	423 (92.8%)
Patients maintained with Q16W dosing interval	-	-	139 (89.1%)	-
Patients with Q12W or longer dosing interval as the last intended dosing interval[b]	-	262 (87.3%)	146 (93.6%)	408 (89.5%)
Patients with Q16W dosing interval as the last intended dosing interval[b]	-	-	136 (87.2%)	-
Patients on a dosing interval shortened to Q8W at week 16	-	3 (1.0%)	1 (0.6%)	4 (0.9%)
Patients on a dosing interval shortened to Q8W at week 20	-	12 (4.0%)	3 (1.9%)	15 (3.3%)
Patients on a dosing interval shortened at any time	-	27 (9.0%)	17 (10.9%)	44 (9.6%)
Patients on a dosing interval shortened to Q8W at any time	-	27 (9.0%)	6 (3.8%)	33 (7.2%)
Patients on a dosing interval shortened to Q12W at any time[c]	-	-	13 (8.3%)	-

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

[a]Study drugs given at week 48 or beyond were not included in this table.

[b]Refers to the patient's assigned interval at week 48.

[c]Includes the patients in whom dosing intervals were shortened only to Q12 as well as the patients in whom dosing intervals were shortened to Q12 and further shortened to Q8.

Source: PHOTON Clinical Study Report (week 60).

Clinical efficacy results from the PHOTON study: 60-week results

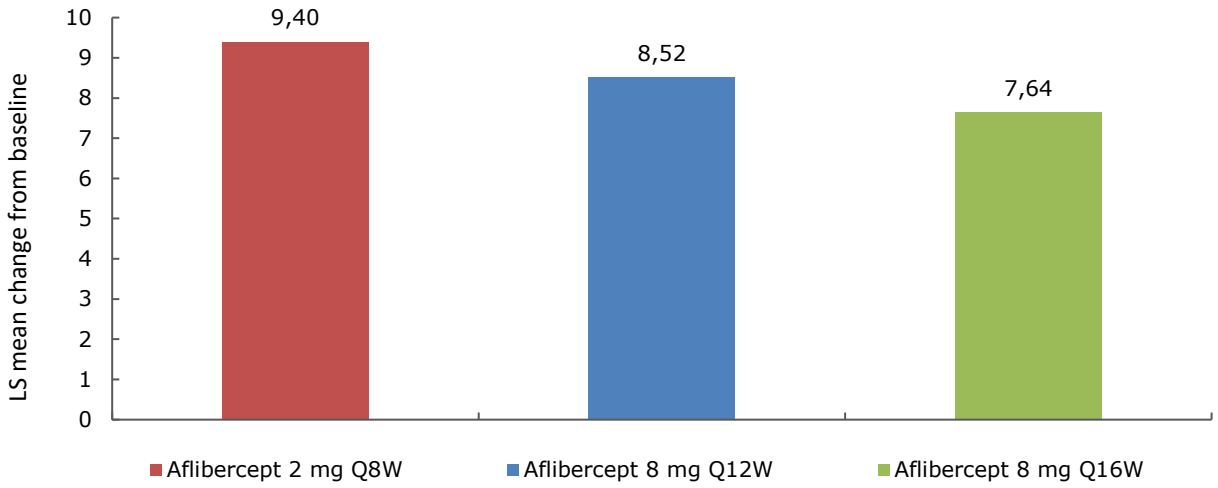
The efficacy demonstrated at week 48 in both aflibercept 8 mg treatment groups was maintained at week 60:

- The key secondary endpoint (mean change in BCVA at week 60) demonstrated that the non-inferiority in 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
- The LS mean changes from baseline in CRT at week 60 were similar across all treatment groups (-181.95 in the aflibercept 8 mg Q12W group, -166.26 in the aflibercept 8 mg Q16W group, and -194.16 in the aflibercept 2 mg Q8W group)

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 PHOTON study, the non-inferiority to aflibercept 2 mg Q8W was maintained at week 60 for both aflibercept 8 mg dosing schedules in terms of LS mean improvement from BCVA as measured by the ETDRS letter score at week 60, using the non-inferiority margin of 4 letters. The analysis of the change from baseline in BCVA resulted in LS mean changes from baseline to week 60 of 8.52 letters in the aflibercept 8 mg Q12W group compared with 9.40 letters in the aflibercept 2 mg Q8W group (the p value for non-inferiority was 0.0003) and 7.64 letters in the aflibercept 8 mg Q16W group (the p value for non-inferiority versus the aflibercept 2 mg Q8W group was 0.0122) (Figure 5 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 the PHOTON Clinical Study Report (week 60).



BCVA=best corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; LS=least square; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

Source: PHOTON Clinical Study Report (week 60): Table 15.

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

	Aflibercept 2 mg	Aflibercept 8 mg	
	Q8W	Q12W	Q16W
Full analysis set	N=167	N=328	N=163
Number of patients with week 60 data	133	252	138
Baseline mean	61.47	63.63	61.44
Mean (SD) change from baseline	9.62 (9.58)	9.05 (9.27)	7.96 (9.14)
LS mean (SE) change from baseline	9.40 (0.77)	8.52 (0.63)	7.64 (0.75)
p value of 1-sided test for non-inferiority at a margin of 4 letters	-	0.0003	0.0122
Difference in LS mean vs aflibercept 2 mg Q8W (95% CI)	-	-0.88 (-2.67, 0.91)	-1.76 (-3.71, 0.19)

BCVA=best -corrected visual acuity; CI=confidence interval; CRT=central retinal thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; FAS=full analysis set; LS=least square; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; SD=standard deviation; SE=standard error.

Source: PHOTON Clinical Study Report (week 60): Table 15.

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

Table 10 PHOTON study: 60-week exploratory endpoints

Exploratory endpoints through week 60, Full analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg (*p value versus aflibercept 2 mg Q8W*) Q12W N=328	*p value*[a]	Q16W N=163	*p value*[a]
Proportion of patients who[a]					
▪ Gained ≥15 letters in BCVA	26.1%	21.5%	*0.2112*	16.0%	*0.0143*
▪ Gained ≥10 letters in BCVA	49.7%	40.8%	*NR*	34.4%	*NR*
▪ Gained ≥5 letters in BCVA	72.1%	69.6%	*NR*	64.4%	*NR*
▪ Lost ≥15 letters in BCVA	0.6%	2.1%	*NR*	0.6%	*NR*
▪ Lost ≥10 letters in BCVA	2.4%	3.4%	*NR*	3.4%	*NR*
▪ Lost ≥5 letters in BCVA	6.1%	6.4%	*NR*	3.1%	*NR*
LS mean change from baseline in CRT (µm)[b]	-194.16	-181.95	*0.1332*	-166.26	*0.0060*

BCVA=best corrected visual acuity; CMH=Cochran-Mantel-Haenszel; CRT=central retinal thickness; LS=least square; MMRM=Mixed Models for Repeated Measures; NR=not reported; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks;.

[a]Nominal p value for the 2-sided CMH superiority test.

[b]An MMRM was used with baseline CRT measurement as a covariate; treatment group and the stratification variables [geographic region (Japan versus Rest of World), baseline CRT from the reading centre (<400 µm versus ≥400 µm), prior treatment for diabetic macular oedema per electronic data capture (yes versus no)] as fixed factors; and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.

Change from baseline in CRT for aflibercept 8 mg (Q12W and Q16W) were non-inferior to aflibercept 2 mg at week 60

Overall, the LS mean changes from baseline in CRT at week 60 were similar across all treatment groups (-181.95 in the aflibercept 8 mg Q12W group, -166.26 in the aflibercept 8 mg Q16W group, and -194.16 in the aflibercept 2 mg Q8W group; Proportion of patients losing ≥15 letters at week 60 were comparable between 8 mg dosing groups and the group treated with aflibercept 2 mg

Table 10). Although reductions from baseline in CRT were consistently observed at all time points, some fluctuation in mean CRT was seen in all treatment groups with attenuation in magnitude over the course of 60 weeks. (The small fluctuations are not considered to be clinically relevant given the demonstration of the non-inferiority in visual acuity.)

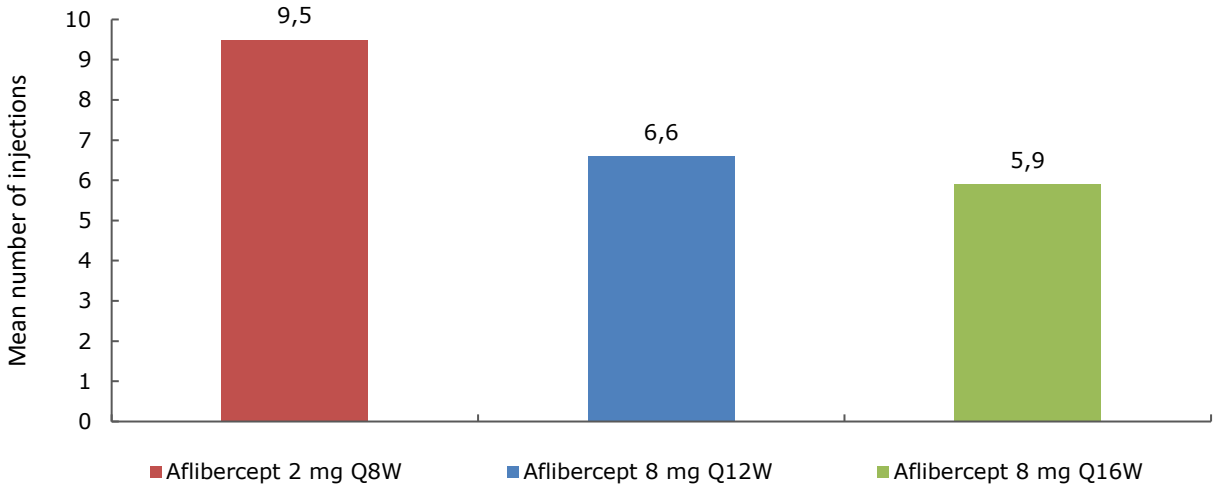
Mean number of injections at week 60 were numerical lower for patients treated with aflibercept 8 mg

Over the 60-week period, patients treated with aflibercept 8 mg received fewer injections versus patients treated with aflibercept 2 mg. The mean number of injections over 60 weeks was 6.6 in the aflibercept 8 mg Q12W group, 5.9 in the aflibercept 8 mg Q16W group, and 9.5 in the aflibercept 2 mg Q8W group (**Figure 6**).

Figure 6 Mean number of aflibercept injections through week 60

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

Source: PHOTON Clinical Study Report (week 60): Table 12.



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 patients maintained with Q16W or longer treatment interval through week 60 in the Q16W group

The majority of patients from the aflibercept 8 mg Q16W group (85.5%) were maintained on the assigned dosing interval through week 60 (Table 11).

Proportion of patients maintained with Q12W or longer treatment interval through week 60 in the Q12W and Q16W groups

The majority of patients from the aflibercept 8 mg Q12W group (90.3%) and the Q16W group (93.4%) were maintained on the Q12W or longer dosing interval through week 60. In the pooled aflibercept 8 mg group, a

substantial majority (91.4%) of patients were maintained on the Q12W or longer dosing interval through week 60 (Table 11).

Proportion of patients with an assigned injection interval of ≥12, ≥16 or ≥20 weeks based on assessment at the last injection visit

The proportion of patients with Q12W or longer treatment interval as the last treatment interval at week 60 was 89.5% in the aflibercept 8 mg Q12W and 87.1% in the Q16W group. The proportion of patients with Q16W as the last treatment interval at week 60 was 42.6% in the aflibercept 8 mg Q12W and 81.6% in the aflibercept 8 mg Q16W group. Furthermore, 34.2% of patients in the aflibercept 8 mg Q16W group were assigned to Q20W as the last intended dosing interval (Table 11).

Table 11 Summary of treatment exposure in the study eye through week 60

	Aflibercept 2 mg Q8W	Aflibercept 8 mg		
		Q12W	Q16W	Pooled
Assessment at the last injection visit[a]	N=155	N=289	N=152	N=441
Patients maintained with Q12W or longer dosing interval	-	261 (90.3%)	142 (93.4%)	403 (91.4%)
Patients maintained with Q16W dosing interval	-	-	130 (85.5%)	-
Patients with Q12W or longer dosing interval as the last intended dosing interval[b]	-	136 (89.5%)	384 (87.1%)	248 (85.8%)
Patients with Q16W dosing interval as the last intended dosing interval[b]	-	123 (42.6%)	124 (81.6%)	247 (56.0%)
Patients with Q20W dosing interval as the last intended dosing interval[c]	-	0	52 (34.2%)	52 (11.8%)
Patients on a dosing interval shortened to Q8W at week 16	-	3 (1.0%)	1 (0.7%)	4 (0.9%)
Patients on a dosing interval shortened to Q8W at week 20	-	12 (4.2%)	3 (2.0%)	15 (3.4%)
Patients on a dosing interval shortened at any time	-	28 (9.7%)	22 (14.5%)	50 (11.3%)
Patients on a dosing interval shortened to Q8W at any time	-	28 (9.7%)	10 (6.6%)	38 (8.6%)
Patients on a dosing interval shortened to Q12W at any time (without shortening to Q8W)	-	-	12 (7.9%)	20 (4.5%)
Patients never on an extended-dosing interval	155 (100%)	156 (54.0%)	93 (61.2%)	249 (56.5%)
Patients on an extended-dosing interval at any time	0	133 (46.0%)	59 (38.8%)	192 (43.5%)

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

[a]Study drugs given at week 60 or beyond were not included in this table.

[b]Refers to the patient's assigned interval at week 60.

[c]Includes the patients in whom dosing intervals were shortened only to Q12 as well as the patients in whom dosing intervals were shortened to Q12 and further shortened to Q8.

Source: PHOTON Clinical Study Report (week 60).

Clinical efficacy results from the PHOTON study: 96-week results

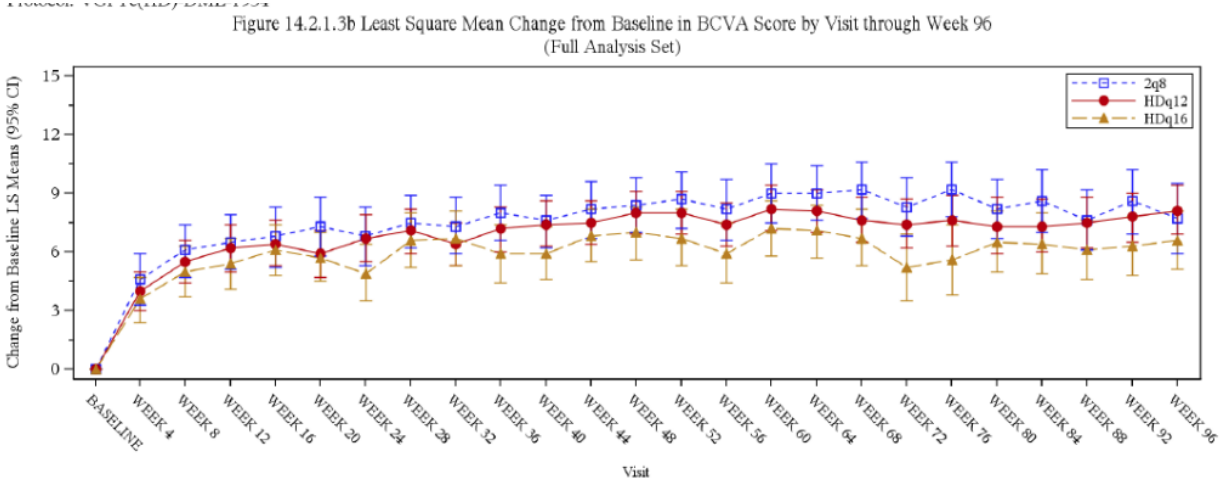
In the PHOTON study, the non-inferiority to aflibercept 2 mg Q8W was maintained at week 96 for both aflibercept 8 mg dosing schedules in terms of LS mean improvement from BCVA as measured by the ETDRS letter score at week 96, using the non-inferiority margin of 4 letters. The analysis of the change from baseline in BCVA resulted in LS mean changes from baseline to week 96 of 8.15 letters in the aflibercept 8 mg Q12W group compared with 7.70 letters in the aflibercept 2 mg Q8W group (the p value for non-inferiority was <0.0001) and 6.59 letters in the aflibercept 8 mg Q16W group (the p value for non-inferiority versus the aflibercept 2 mg Q8W group was 0.0044) (Table 12 and Figure 7).

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

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

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 96 data	DF	Contrast [a]	t-value	1-sided NI p-value [b]	1-sided superiority p-value	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	8.15 (0.63)	8.82 (9.93)	63.63	222	386.7	HDq12 2q8	4.3752	<0.0001	0.3282	0.45 (-1.55, 2.45)
HDq16 (N=163)	6.59 (0.77)	7.50 (9.86)	61.44	127	391.5	HDq16 2q8	2.6296	0.0044	0.8431	-1.11 (-3.27. 1.05)
2q8 (N=167)	7.70 (0.89)	8.41 (11.10)	61.47	124						

Figure 7 Least square mean change from baseline in BCVA score by visit through week 96



2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP
Least square mean (LSM) was generated from a mixed model for repeated measurements (MMRM), with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400 microns vs. >=400 microns], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.
/sasdata/Data/Production/BDM/VGFT/VGFT-HD-DME/VGFTe-DME-1934/Week96/Analysis_CSR/Programs/TFL/f_eff_lsm.sas (junjia.bai 14JUL2023 18:12 SAS Linux 9.4)

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

Table 13 Proportion of patients losing ≥15 letters at week 96

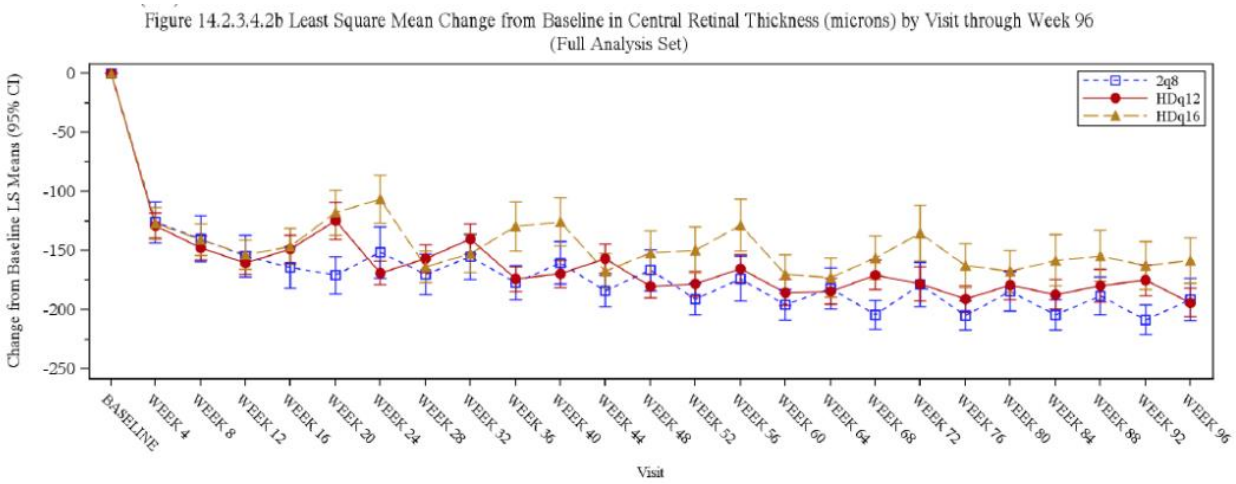
Endpoint	Visit	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)
Lost >= 15 letters	Week 88	4/165 (2.4%)	11/326 (3.4%)	1/163 (0.6%)
	Week 92	4/165 (2.4%)	11/326 (3.4%)	3/163 (1.8%)
	Week 96	6/165 (3.6%)	11/326 (3.4%)	2/163 (1.2%)

Change from baseline in CRT for aflibercept 8 mg (Q12W and Q16W) were non-inferior to aflibercept 2 mg at week 96

Table 14 Change from baseline in CRT at week 96

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 96 data	DF	Contrast [a]	t-value	p-value [b]	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	-193.99 (6.09)	-185.28 (146.49)	449.15	215	372.1	HDq12-2q8	-0.2633	0.7925	-2.72 (-23.05. 17.61)
HDq16 (N=163)	-158.39 (9.67)	-154.98 (144.92)	460.32	124	366.0	HDq16 2q8	2.5771	0.0104	32.87 (7.79. 57.95)
2q8 (N=167)	-191.26 (9.12)	-186.95 (146.28)	457.25	122					

Figure 8 Least square mean change from baseline in Central Retinal Thicknes (microns) by visit through week 96



2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
Intercurrent events (ICE) were handled according to Table 1 of SAP
Least square mean (LSM) was generated from a mixed model for repeated measurements (MMRM), with baseline CRT measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400 microns vs. >=400 microns], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.
/sasdata/Data/Production/BDM/VGFT/VGFT-HD-DME/VGFTe-DME-1934/Week96/Analysis_CSR/Programs/TFL/f_eff_lsm.sas (junjia.bai 14JUL2023 18:12 SAS Linux 9.4)

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

Table 15 Mean number of injections through week 96

	2q8 N=139	HDq12 N=256	HDq16 N=139	All HD N=395
Summary of active injections				
n	139	256	139	395
Mean (SD)	13.8(0.62)	9.5 (0.98)	7.8(1.13)	8.9(1.30)
Median	14.0	9.0	8.0	9.0
Q1:Q3	14.0:14.0	90:100	7.0:8.0	80:10.0
Mis Max	10:14	8:13	6:13	6:13

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

Proportion of patients with an assigned injection interval of ≥12, ≥16 or ≥20 weeks based on assessment at the last injection visit

Table 16 Summary of treatment exposure in Study Eye through week 96

	2q8 N=139	HDq12 N=256	HDq16 N=139	All HD N=395
Patients maintained with q12 or longer dosing interval, n (%)	0	224 (87.5%)	129 (92.8%)	353 (89.4%)
Patients maintained with q16 or longer dosing interval, n (%)	0	0	116 (83.5%)	116 (29.4%)
Patients maintained and extended to q20 or longer dosing interval, n (%)	0	108 (42.2%)	63 (45.3%)	171 (43.3%)
Patients maintained and extended to q24 dosing interval, n (%)	0	61 (23.8%)	44 (31.7%)	105 (26.6%)
Patients with q12 or longer dosing interval as the last [b] intended dosing interval, n (%)	0	235 (91.8%)	132(95.0%)	367 (92.9%)
Patients with q16 or longer dosing interval as the last [b] intended dosing interval, n (%)	0	164 (64.1%)	122 (87.8%)	286 (72.4%)
Patients with q20 or longer dosing interval as the last [b] intended dosing interval, n (%)	0	10 (43.0%)	5(46.8%)	175 (44.3%)
Patients with q24 dosing interval as the last [b] intended dosing interval, n (%)	0	61 (23.8%)	45 (32.4%)	106 (26.8%)
Patients shortened to q8 dosing interval at week 16, n (%)	0	3 (1.2%)	1 (0.7%)	4 (1.0%)
Patients shortened to q8 dosing interval at week 20, n (%)	0	11 (4.3%)	2 (1.4%)	13 (3.3%)
Patients with a shortened dosing interval anytime, n (%)	0	36 (14.1%)	24 (17.3%)	60 (15.2%)
Patients shortened to q8 dosing interval anytime, n (%)	0	32 (12.5%)	10 (7.2%)	42 (10.6%)
Patients shortened to q12 dosing interval anytime (without shortening to q8), n (%)	0	0	13 (9.4%)	13 (3.3%)
Patients never extended dosing interval, n (%)	139 (100%)	81 (31.6%)	65 (46.8%)	146 (37.0%)

Patients with an extended dosing interval anytime, n (%)	0	175 (68.4%)	74 (53.2%)	249 (63.0%)
Patients extended to q20 dosing interval anytime, n (%)	0	111 (43.4%)	66 (47.5%)	177 (44.8%)
Patients extended to q20 dosing interval and shortened back to q16, n (%)	0	(0.4%)	1 (0.7%)	2 (0.5%)
Patients extended to q20 dosing interval and maintained at q20, n (%)	0	14 (5.5%)	12 (8.6%)	26 (6.6%)
Patients extended to q20 dosing interval and extended to q24, n (%)	0	61 (23.8%)	45 (32.4%)	106 (26.8%)
Patients extended to q20 dosing interval at their last visit [c], n (%)	0	35 (13.7%)	8 (5.8%)	43 (10.9%)

[b] Based on dose regimen dose modification (DRM) criteria assessed at the last visit with an active injection before week 96 [i.e., including DRM criteria until week 92.

[c] This includes patients extended to q20 at their last active dosing visit prior to week 96 and hence it is unknown if theyu were maintained, extended, or shorteneded ater that visit.

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

PHOTON study: 48-week safety results for aflibercept 8 mg were similar to aflibercept 2 mg

Proportion of patients with any ocular treatment-emergent adverse events and any non-ocular treatment-emergent adverse events at week 48

The proportions of patients who experienced TEAEs in the aflibercept 8 mg Q12W (69.2%) and Q16W (72.4%) treatment groups (70.3% in the pooled aflibercept 8 mg Q12W and Q16W treatment group) were numerically higher compared with the aflibercept 2 mg Q8W (63.5%) treatment group. The proportions of patients with any ocular TEAEs through week 48 were similar across all 3 treatment groups (40.9% in the aflibercept 8 mg Q12W, 38.7% in the aflibercept 8 mg Q16W, and 40.1% in the pooled aflibercept 8 mg Q12W and Q16W treatment group versus 38.3% in the aflibercept 2 mg Q8W group).

The proportions of patients with any ocular TEAEs in study eye were also similar across all 3 aflibercept groups (31.7% in the aflibercept 8 mg Q12W, 29.4% in the aflibercept 8 mg Q16W, and 31.0% in the pooled aflibercept 8 mg Q12W and Q16W treatment group, compared with 27.5% in the aflibercept 2 mg Q8W group), and most of the reported ocular TEAEs in the study eye were mild. In the pooled aflibercept 8 mg treatment group, the proportions of patients with any ocular TEAE in the study eye of mild, moderate, and severe intensity were 23.6%, 6.7%, and 0.6%, respectively. In the aflibercept 2 mg Q8W group, these proportions were 21.0%, 6.0%, and 0.6%, respectively.

The proportions of patients with TEAEs related to intraocular inflammation in the study eye were low across all treatment groups. TEAEs related to intraocular inflammation were reported in 1.2% of patients from the aflibercept 8 mg Q12W group (no intraocular inflammation events reported in the aflibercept 8 mg Q16W group) versus 0.6% of patients from the aflibercept 2 mg Q8W group. None of the reported intraocular inflammation events were serious. Furthermore, the proportions of patients with increased IOP were similar between the treatment groups. Increased IOP was reported in 1.6% of patients in the pooled aflibercept 8 mg Q12W and Q16W treatment group and 3.6% of patients in the aflibercept 2 mg Q8W group.

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

Any TEAEs judged to be related to the study drug were reported in 1.2% of patients in the pooled Q12W and Q16W treatment group and in 1.8% of patients in the aflibercept 2 mg Q8W group. Any ocular TEAEs judged to be related to the study drug affected 1.0% of patients in the pooled Q12W and Q16W treatment group and 1.8% of patients in the aflibercept 2 mg Q8W group.

Ocular TEAEs in the study eye, judged to be related to the study drug, were reported in 1.0% of patients in the pooled Q12W and Q16W treatment group and in 1.8% of patients in the aflibercept 2 mg Q8W group. Increased IOP was the only ocular TEAE in the study eye, judged to be related to the study drug, that was reported in more than 1 patient in any treatment group.

Proportion of patients 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 the study drug were similar across all 3 treatment groups [1.2% in the aflibercept 8 mg Q16W group and 2.4% in the aflibercept 8 mg Q12W group (2.0% in the pooled aflibercept 8 mg Q12W and Q16W treatment group) versus 1.2% in the aflibercept 2 mg Q8W group] (Table 17). Any ocular TEAEs leading to discontinuation of the study drug affected only 0.6% of patients in the aflibercept 8 mg Q12W treatment group and none of the patients in the remaining treatment groups.

Ocular TEAEs in the study eye that resulted in discontinuation of the study drug affected only 0.6% of patients in the aflibercept 8 mg Q12W group and none of the patients in the remaining treatment groups.

Proportion of patients 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 the aflibercept 8 mg groups and aflibercept 2 mg group. Intravitreal injection procedure–related TEAEs in the study eye were reported in 10.8% of patients in the pooled aflibercept 8 mg group and in 9.0% of patients 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 >2 patients in similar proportions of patients across the 3 treatment groups, were conjunctival haemorrhage, vitreous floaters, eye pain, and increased IOP.

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

The proportion of patients with ocular treatment-emergent serious adverse events (TESAEs) in the study eye was low, and a total of 5 TESAEs only were reported in 4 patients (1 patient in the aflibercept 2 mg Q8W group with ulcerative keratitis, 1 patient in the aflibercept 8 mg Q12W group with cataract subcapsular, 1 patient in the aflibercept 8 mg Q12W group with IOP increased, and 1 patient in the aflibercept 8 mg Q16W group with retinal detachment and vitreous haemorrhage) (Table 18). A total of 9 ocular TESAEs in the fellow eye were reported in 8 patients, and none of these TESAEs were considered related to the study drug.

Non-ocular TESAEs were reported in 13.5% of patients in the aflibercept 8 mg Q16W group and 15.9% of patients in the aflibercept 8 mg Q12W group (15.1% in the pooled aflibercept 8 mg Q12W and Q16W treatment group) versus 15.6% of patients in the aflibercept 2 mg Q8W group. The majority of these TESAEs were reported in single patients only.

Table 17 Overall summary of all adverse events through week 48

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
Any AE	108 (64.7%)	231 (70.4%)	120 (73.6%)	351 (71.5%)
Any pre-treatment AE[a]	7 (4.2%)	14 (4.3%)	8 (4.9%)	22 (4.5%)
Any TEAE[b]	106 (63.5%)	227 (69.2%)	118 (72.4%)	345 (70.3%)
Any post-treatment AE[c]	0	5 (1.5%)	2 (1.2%)	7 (1.4%)
Any ocular TEAE	64 (38.3%)	134 (40.9%)	63 (38.7%)	197 (40.1%)
Study eye	46 (27.5%)	104 (31.7%)	48 (29.4%)	152 (31.0%)
Eye disorders	41 (24.6%)	94 (28.7%)	46 (28.2%)	140 (28.5%)
▪ Cataract	2 (1.2%)	5 (1.5%)	8 (4.9%)	13 (2.6%)
▪ Cataract nuclear	2 (1.2%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Conjunctival haemorrhage	6 (3.6%)	14 (4.3%)	6 (3.7%)	20 (4.1%)
▪ Corneal erosion	0	0	2 (1.2%)	2 (0.4%)
▪ Diabetic retinal oedema	3 (1.8%)	9 (2.7%)	3 (1.8%)	12 (2.4%)
▪ Dry eye	1 (0.6%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
▪ Epiretinal membrane	2 (1.2%)	1 (0.3%)	0	1 (0.2%)
▪ Eye irritation	1 (0.6%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
▪ Eye pain	4 (2.4%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
▪ Keratitis	0	0	2 (1.2%)	2 (0.4%)
▪ Macular oedema	2 (1.2%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
▪ Ocular hypertension	1 (0.6%)	4 (1.2%)	0	4 (0.8%)
▪ Posterior capsule opacification	2 (1.2%)	0	2 (1.2%)	2 (0.4%)
▪ Punctate keratitis	1 (0.6%)	5 (1.5%)	6 (3.7%)	11 (2.2%)
▪ Retinal aneurysm	2 (1.2%)	0	1 (0.6%)	1 (0.2%)
▪ Retinal exudates	2 (1.2%)	1 (0.3%)	1 (0.6%)	2 (0.4%)

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
▪ Retinal haemorrhage	1 (0.6%)	0	6 (3.7%)	6 (1.2%)
▪ Vision blurred	3 (1.8%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
▪ Visual acuity reduced	3 (1.8%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
▪ Visual impairment	1 (0.6%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
▪ Vitreous detachment	2 (1.2%)	11 (3.4%)	3 (1.8%)	14 (2.9%)
▪ Vitreous floaters	4 (2.4%)	16 (4.9%)	3 (1.8%)	19 (3.9%)
▪ Vitreous haemorrhage	1 (0.6%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
▪ Infections and infestations	1 (0.6%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
▪ Conjunctivitis	0	0	2 (1.2%)	2 (0.4%)
▪ Injury, poisoning, and procedural complications	2 (1.2%)	4 (1.2%)	1 (0.6%)	5 (1.0%)
▪ Corneal abrasion	2 (1.2%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
▪ Investigations	7 (4.2%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
▪ Intraocular pressure increased	6 (3.6%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
Fellow eye	44 (26.3%)	78 (23.8%)	45 (27.6%)	123 (25.1%)
Any non-ocular TEAE	79 (47.3%)	174 (53.0%)	95 (58.3%)	269 (54.8%)
Any study drug–related TEAE	3 (1.8%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
Any study drug–related ocular TEAE	3 (1.8%)	5 (1.5%)	0	5 (1.0%)
Study eye	3 (1.8%)	5 (1.5%)	0	5 (1.0%)
▪ Intraocular pressure increased	0	3 (0.9%)	0	3 (0.6%)
Fellow eye	0	0	0	0
Any study drug–related non-ocular TEAE	0	0	1 (0.6%)	1 (0.2%)
Any injection procedure–related TEAE	18 (10.8%)	43 (13.1%)	13 (8.0%)	56 (11.4%)
Any injection procedure–related ocular TEAE	18 (10.8%)	43 (13.1%)	13 (8.0%)	56 (11.4%)
Study eye	15 (9.0%)	40 (12.2%)	13 (8.0%)	53 (10.8%)
Eye disorders	10 (6.0%)	32 (9.8%)	12 (7.4%)	44 (9.0%)

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
▪ Conjunctival haemorrhage	6 (3.6%)	10 (3.0%)	5 (3.1%)	15 (3.1%)
▪ Vitreous floaters	1 (0.6%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
▪ Eye pain	1 (0.6%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
▪ Intraocular pressure increased	4 (2.4%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
Fellow eye	5 (3.0%)	7 (2.1%)	5 (3.1%)	12 (2.4%)
Any injection procedure–related non-ocular TEAE	0	2 (0.6%)	1 (0.6%)	3 (0.6%)
Any study conduct–related TEAE	2 (1.2%)	6 (1.8%)	0	6 (1.2%)
Any study conduct–related ocular TEAE	0	2 (0.6%)	0	2 (0.4%)
Study eye	0	2 (0.6%)	0	2 (0.4%)
Fellow eye	0	0	0	0
Any study conduct–related non-ocular TEAE	2 (1.2%)	4 (1.2%)	0	4 (0.8%)
Any TEAE related to aflibercept 2 mg in fellow eye	2 (1.2%)	1 (0.3%)	3 (1.8%)	4 (0.8%)
Any ocular TEAE related to aflibercept 2 mg in fellow eye	2 (1.2%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
Study eye	0	0	0	0
Fellow eye	2 (1.2%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
Any non-ocular TEAE related to aflibercept 2 mg in fellow eye	0	0	1 (0.6%)	1 (0.2%)
Any serious pre-treatment AE	0	1 (0.3%)	0	1 (0.2%)
Any serious post-treatment AE	0	2 (0.6%)	2 (1.2%)	4 (0.8%)
Any serious TEAE	31 (18.6%)	55 (16.8%)	24 (14.7%)	79 (16.1%)
Any ocular serious TEAE	5 (3.0%)	5 (1.5%)	2 (1.2%)	7 (1.4%)
Study eye	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Fellow eye	4 (2.4%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
Any non-ocular serious TEAE	26 (15.6%)	52 (15.9%)	22 (13.5%)	74 (15.1%)
Any study drug–related serious TEAE	0	0	0	0
Any injection procedure–related serious TEAE	0	1 (0.3%)	0	1 (0.2%)

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
Any injection procedure–related ocular serious TEAE	0	1 (0.3%)	0	1 (0.2%)
Study eye	0	1 (0.3%)	0	1 (0.2%)
Fellow eye	0	0	0	0
Any injection procedure–related non-ocular serious TEAE	0	0	0	0
Any study conduct–related serious TEAE	0	0	0	0
Any serious TEAE related to aflibercept 2 mg in fellow eye	0	0	0	0
Any TEAE leading to discontinuation of study drug	2 (1.2%)	8 (2.4%)	2 (1.2%)	10 (2.0%)
Any ocular TEAE leading to discontinuation of study drug	0	2 (0.6%)	0	2 (0.4%)
Study eye	0	2 (0.6%)	0	2 (0.4%)
Fellow eye	0	0	0	0
Any non-ocular TEAE leading to discontinuation of study drug	2 (1.2%)	6 (1.8%)	2 (1.2%)	8 (1.6%)
Any death	4 (2.4%)	9 (2.7%)	3 (1.8%)	12 (2.4%)
Any pre-treatment AE with outcome death	0	0	0	0
Any TEAE with outcome death	4 (2.4%)	8 (2.4%)	2 (1.2%)	10 (2.0%)
Any post-treatment AE with outcome death	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Any treatment-emergent adjudicated APTC event	6 (3.6%)	8 (2.4%)	7 (4.3%)	15 (3.1%)
Any treatment-emergent intraocular inflammation event in the study eye	1 (0.6%)	4 (1.2%)	0	4 (0.8%)
Any treatment-emergent hypertension event	20 (12.0%)	36 (11.0%)	23 (14.1%)	59 (12.0%)
Any treatment-emergent nasal mucosal event	0	0	0	0
Maximum severity (% per treatment group)				
Maximum severity for any ocular TEAE in study eye	46 (27.5%)	104 (31.7%)	48 (29.4%)	152 (31.0%)
Mild severity for any ocular TEAE in study eye	35 (21.0%)	75 (22.9%)	41(25.2%)	116 (23.6%)
Moderate severity for any ocular TEAE in study eye	10 (6.0%)	27 (8.2%)	6 (3.7%)	33 (6.7%)
Any severe ocular TEAE in study eye	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
Maximum severity for any ocular TEAE in fellow eye	44 (26.3%)	78 (23.8%)	45 (27.6%)	123 (25.1%)
Mild severity for any ocular TEAE in fellow eye	31 (18.6%)	58 (17.7%)	33 (20.2%)	91 (18.5%)
Moderate severity for any ocular TEAE in fellow eye	10 (6.0%)	17 (5.2%)	12 (7.4%)	29 (5.9%)
Any severe ocular TEAE in fellow eye	3 (1.8%)	3 (0.9%)	0	3 (0.6%)
Mild severity for any non-ocular TEAE	34 (20.4%)	78 (23.8%)	49 (30.1%)	127 (25.9%)
Moderate severity for any non-ocular TEAE	27 (16.2%)	61 (18.6%)	32 (19.6%)	93 (18.9%)
Any severe non-ocular TEAE	18 (10.8%)	35 (10.7%)	14 (8.6%)	49 (10.0%)
Maximum severity for any ocular serious TEAE in study eye	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Mild severity for any ocular serious TEAE in study eye	0	0	0	0
Moderate severity for any ocular serious TEAE in study eye	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Any severe serious TEAE in study eye	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Maximum severity for any ocular serious TEAE in fellow eye	4 (2.4%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
Mild severity for any ocular serious TEAE in fellow eye	0	0	0	0
Moderate severity for any ocular serious TEAE in fellow eye	2 (1.2%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Any severe ocular serious TEAE in fellow eye	2 (1.2%)	1 (0.3%)	0	1 (0.2%)
Maximum severity for any non-ocular serious TEAE	26 (15.6%)	52 (15.9%)	22 (13.5%)	74 (15.1%)
Mild severity for any non-ocular serious TEAE	2 (1.2%)	2 (0.6%)	0	2 (0.4%)
Moderate severity for any non-ocular serious TEAE	9 (5.4%)	17 (5.2%)	8 (4.9%)	25 (5.1%)
Any severe non-ocular serious TEAE	15 (9.0%)	33 (10.1%)	14 (8.6%)	47 (9.6%)

AE=adverse event; APTC=Antiplatelet Trialists' Collaboration; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; TEAE=treatment-emergent adverse event.

The percentage was based on the number of patients in each treatment group as denominator.

[a]A pre-treatment AE was an AE starting from signing the informed consent form to before the first dose of study drug.

[b]A TEAE was an AE starting after the first dose of study drug to the last dose of study drug (active or sham) plus 30 days. Additionally, for patients who were still participating in the study (i.e., had not been withdrawn) as of the week 48 visit, all AEs up through the date of the last visit were to be considered treatment-emergent.

[c]A post-treatment AE was an AE starting after the end of the on-treatment (TEAE) period.

Source: PHOTON Clinical Study Report (week 48).

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

Primary system organ class Preferred term MedDRA version 25.0	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
Ocular TESAEs in study eye				
Ulcerative keratitis	1 (0.6%)	0	0	0
Cataract subcapsular	0	1 (0.3%)	0	0
Intraocular pressure increased	0	1 (0.3%)	0	0
Retinal detachment	0	0	1 (0.6%)	0
Vitreous haemorrhage	0	0	1 (0.6%)	0
Non-ocular TESAEs reported in ≥2 patients				
Number of patients with at least one such AE	26 (15.6%)	52 (15.9%)	22 (13.5%)	74 (15.1%)
Blood and lymphatic system disorders	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Anaemia	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Cardiac disorders	9 (5.4%)	13 (4.0%)	4 (2.5%)	17 (3.5%)
▪ Acute left ventricular failure	3 (1.8%)	1 (0.3%)	0	1 (0.2%)
▪ Acute myocardial infarction	2 (1.2%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Cardiac arrest	2 (1.2%)	2 (0.6%)	0	2 (0.4%)
▪ Cardiac failure	1 (0.6%)	2 (0.6%)	0	2 (0.4%)
▪ Coronary artery disease	1 (0.6%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
▪ Coronary artery occlusion	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Myocardial infarction	2 (1.2%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
General disorders and administration-site conditions	2 (1.2%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
▪ Chest pain	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Infections and infestations	8 (4.8%)	13 (4.0%)	2 (1.2%)	15 (3.1%)
▪ COVID-19	0	3 (0.9%)	1 (0.6%)	4 (0.8%)
▪ COVID-19 pneumonia	2 (1.2%)	2 (0.6%)	0	2 (0.4%)
▪ Gangrene	2 (1.2%)	0	0	0
▪ Pneumonia	1 (0.6%)	4 (1.2%)	0	4 (0.8%)
Metabolism and nutrition disorders	5 (3.0%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
▪ Hyponatraemia	2 (1.2%)	0	0	0
Musculoskeletal and connective tissue disorders	0	3 (0.9%)	2 (1.2%)	5 (1.0%)
▪ Neuropathic arthropathy	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Nervous system disorders	2 (1.2%)	5 (1.5%)	6 (3.7%)	11 (2.2%)
▪ Cerebrovascular accident	0	2 (0.6%)	4 (2.5%)	6 (1.2%)
Renal and urinary disorders	0	8 (2.4%)	1 (0.6%)	9 (1.8%)

Primary system organ class Preferred term MedDRA version 25.0	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	 Q16W N=163	 Pooled N=491
▪ Acute kidney injury	0	4 (1.2%)	0	4 (0.8%)
Respiratory, thoracic, and mediastinal disorders	3 (1.8%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
▪ Acute respiratory failure	2 (1.2%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
▪ Pulmonary embolism	0	2 (0.6%)	0	2 (0.4%)

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; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.

Source: PHOTON Clinical Study Report (week 48).

PHOTON study: 60-week safety results for aflibercept 8 mg were similar to aflibercept 2 mg

Proportion of patients with any ocular treatment-emergent adverse events and any non-ocular treatment-emergent adverse events at week 60

The proportions of patients, who experienced TEAEs in the aflibercept 8 mg Q12W (74.7%) and Q16W (77.3%) treatment groups (75.6% in the pooled aflibercept 8 mg Q12W and Q16W treatment group) and in the aflibercept 2 mg Q8W group (73.7%) were similar. The proportions of patients with any ocular TEAEs through week 60 were similar across all 3 treatment groups (44.8% in the aflibercept 8 mg Q12W group, 44.8% in the aflibercept 8 mg Q16W group, 44.8% in the pooled aflibercept 8 mg Q12W and Q16W treatment group, and 43.7% in the aflibercept 2 mg Q8W group)(Table 19).

The proportions of patients with any ocular TEAEs in study eye were also similar across all 3 treatment groups (36.0% in the aflibercept 8 mg Q12W group, 34.4% in the aflibercept 8 mg Q16W group, 35.4% in the pooled aflibercept 8 mg Q12W and Q16W treatment group, and 29.3% in the aflibercept 2 mg Q8W group), and most of the reported ocular TEAEs in the study eye were mild. In the pooled aflibercept 8 mg treatment group, the proportions of participants with any ocular TEAE in the study eye, of mild, moderate, and severe intensity, were 26.9%, 7.9%, and 0.6%, respectively. In the aflibercept 2 mg Q8W group, these proportions were 22.8%, 6.0%, and 0.6%, respectively.

The proportions of patients with TEAEs related to intraocular inflammation in the study eye were low and were similar across the treatment groups, and none of these TEAEs were serious. Furthermore, the proportions of patients with increased IOP were similar between the treatment groups. Increased IOP was present in 1.6% of patients in the pooled aflibercept 8 mg Q12W and Q16W treatment group and 3.6% of patients in the aflibercept 2 mg Q8W group. (Table 19)

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

Any TEAEs judged to be related to the study drug were reported in 1.4% of patients in the pooled Q12W and Q16W treatment group and in 1.8% of patients in the aflibercept 2 mg Q8W group. Any ocular TEAEs judged to be related to the study drug affected 1.2% of patients in the pooled Q12W and Q16W treatment group and in 1.8% of patients in the aflibercept 2 mg Q8W group.

Ocular TEAEs in the study eye judged to be related to the study drug were reported in 1.2% of patients in the pooled Q12W and Q16W treatment group and in 1.8% of patients in the aflibercept 2 mg Q8W group. Increased IOP was the only ocular TEAE in the study eye, judged to be related to the study drug, that was reported for more than 1 patient in any treatment group. (Table 19)

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

The proportions of patients who experienced any TEAEs leading to discontinuation of the study drug were similar across all 3 treatment groups [1.2% in the aflibercept 8 mg Q16W group and 2.7% in the aflibercept 8 mg Q12W group (2.2% in the pooled aflibercept 8 mg Q12W and Q16W treatment group) versus 1.8% in the aflibercept 2 mg Q8W group]. Any ocular TEAEs leading to discontinuation of the study drug affected only 0.6% of patients in the aflibercept 8 mg Q12W treatment group and none of the patients in the remaining treatment groups.

Ocular TEAEs in the study eye that resulted in discontinuation of the study drug affected only 0.6% of patients in the aflibercept 8 mg Q12W group and none of the patients in the remaining treatment groups. (Table 19)

Proportion of patients 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 11.2% of patients in the pooled aflibercept 8 mg group and in 9.6% of patients in the aflibercept 2 mg Q8W group. The most common ocular TEAEs related to intravitreal injection procedure in the study eye, reported in >2 patients, were conjunctival haemorrhage, vitreous floaters, eye pain, and increased IOP. (Table 19)

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

The proportion of patients with ocular TESAEs in the study eye was low and only a total of 5 of these TESAEs, not considered as related to the study drug, were reported in 4 patients [1 in the aflibercept 2 mg Q8W group with ulcerative keratitis, 1 in the aflibercept 8 mg Q12W group with cataract subcapsular, 1 in the aflibercept 8 mg Q12W group with increased IOP (considered as related to injection procedure), and 1 in the aflibercept 8 mg Q16W group with retinal detachment and vitreous haemorrhage]. A total of 11 ocular TESAEs in the fellow eye were reported in 9 patients, and none of these TESAEs were considered related to the study drug.

Non-ocular TESAEs were reported in 16.6% of patients in the aflibercept 8 mg Q16W group and 18.6% of patients in the aflibercept 8 mg Q12W group (17.9% in the pooled aflibercept 8 mg Q12W and Q16W treatment group) versus 19.2% of patients 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=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
Any AE	124 (74.3%)	247 (75.3%)	128 (78.5%)	375 (76.4%)
Any pre-treatment AE[a]	7 (4.2%)	14 (4.3%)	8 (4.9%)	22 (4.5%)
Any TEAE[b]	123 (73.7%)	245 (74.7%)	126 (77.3%)	371 (75.6%)
Any post-treatment AE[c]	0	5 (1.5%)	3 (1.8%)	8 (1.6%)
Any ocular TEAE[d]	73 (43.7%)	147 (44.8%)	73 (44.8%)	220 (44.8%)
Study eye	49 (29.3%)	118 (36.0%)	56 (34.4%)	174 (35.4%)
Eye disorders[e]	43 (25.7%)	108 (32.9%)	54 (33.1%)	162 (33.0%)
▪ Cataract[e]	3 (1.8%)	9 (2.7%)	9 (5.5%)	18 (3.7%)
▪ Cataract nuclear[e]	2 (1.2%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
▪ Cataract subcapsular[e]	1 (0.6%)	5 (1.5%)	0	5 (1.0%)
▪ Conjunctival haemorrhage[e]	6 (3.6%)	14 (4.3%)	7 (4.3%)	21 (4.3%)
▪ Corneal erosion[e]	0	1 (0.3%)	2 (1.2%)	3 (0.6%)
▪ Diabetic retinal oedema[e]	3 (1.8%)	9 (2.7%)	3 (1.8%)	12 (2.4%)
▪ Diabetic retinopathy[e]	1 (0.6%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
▪ Dry eye[e]	1 (0.6%)	4 (1.2%)	3 (1.8%)	7 (1.4%)
▪ Epiretinal membrane[e]	3 (1.8%)	1 (0.3%)	0	1 (0.2%)
▪ Eye irritation[e]	1 (0.6%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
▪ Eye pain[e]	4 (2.4%)	9 (2.7%)	1 (0.6%)	10 (2.0%)
▪ Keratitis[e]	0	0	2 (1.2%)	2 (0.4%)
▪ Macular oedema[e]	2 (1.2%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
▪ Ocular hypertension[e]	1 (0.6%)	4 (1.2%)	0	4 (0.8%)
▪ Posterior capsule opacification[e]	2 (1.2%)	0	2 (1.2%)	2 (0.4%)

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
▪ Punctate keratitis[e]	1 (0.6%)	5 (1.5%)	6 (3.7%)	11 (2.2%)
▪ Retinal aneurysm[e]	2 (1.2%)	0	1 (0.6%)	1 (0.2%)
▪ Retinal exudates[e]	2 (1.2%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Retinal haemorrhage[e]	1 (0.6%)	0	6 (3.7%)	6 (1.2%)
▪ Vision blurred[e]	3 (1.8%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
▪ Visual acuity reduced[e]	3 (1.8%)	3 (0.9%)	2 (1.2%)	5 (1.0%)
▪ Visual impairment[e]	1 (0.6%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
▪ Vitreous detachment[e]	3 (1.8%)	10 (3.0%)	4 (2.5%)	14 (2.9%)
▪ Vitreous floaters[e]	4 (2.4%)	18 (5.5%)	6 (3.7%)	24 (4.9%)
▪ Vitreous haemorrhage[e]	1 (0.6%)	6 (1.8%)	2 (1.2%)	8 (1.6%)
Infections and infestations[e]	3 (1.8%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
▪ Conjunctivitis[e]	1 (0.6%)	0	2 (1.2%)	2 (0.4%)
Injury, poisoning, and procedural complications[e]	2 (1.2%)	4 (1.2%)	1 (0.6%)	5 (1.0%)
▪ Corneal abrasion[e]	2 (1.2%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
Investigations[e]	7 (4.2%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
▪ IOP increased[e]	6 (3.6%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
Fellow eye	52 (31.1%)	91 (27.7%)	52 (31.9%)	143 (29.1%)
Any non-ocular TEAE	96 (57.5%)	195 (59.5%)	104 (63.8%)	299 (60.9%)
Any study drug–related TEAE	3 (1.8%)	6 (1.8%)	1 (0.6%)	7 (1.4%)
Any study drug–related ocular TEAE	3 (1.8%)	6 (1.8%)	0	6 (1.2%)
Study eye	3 (1.8%)	6 (1.8%)	0	6 (1.2%)
Eye disorders	3 (1.8%)	4 (1.2%)	0	4 (0.8%)
▪ Iritis	0	1 (0.3%)	0	1 (0.2%)
▪ Ocular hypertension	0	1 (0.3%)	0	1 (0.2%)
▪ Retinal artery stenosis	1 (0.6%)	0	0	0

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
▪ Vision blurred	1 (0.6%)	0	0	0
▪ Vitreous detachment	1 (0.6%)	0	0	0
▪ Vitreous floaters	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
▪ Vitreous opacities	1 (0.6%)	0	0	0
▪ Vitritis	0	1 (0.3%)	0	1 (0.2%)
Investigations	1 (0.6%)	3 (0.9%)	0	3 (0.6%)
▪ IOP decreased	1 (0.6%)	0	0	0
▪ IOP increased	0	3 (0.9%)	0	3 (0.6%)
Fellow eye	0	0	0	0
Any study drug–related non-ocular TEAE	0	0	1 (0.6%)	1 (0.2%)
Any injection procedure–related TEAE	19 (11.4%)	45 (13.7%)	13 (8.0%)	58 (11.8%)
Any injection procedure–related ocular TEAE	19 (11.4%)	45 (13.7%)	13 (8.0%)	58 (11.8%)
Study eye	16 (9.6%)	42 (12.8%)	13 (8.0%)	55 (11.2%)
Eye disorders	11 (6.6%)	34 (10.4%)	12 (7.4%)	46 (9.4%)
▪ Conjunctival haemorrhage	6 (3.6%)	10 (3.0%)	5 (3.1%)	15 (3.1%)
▪ Eye irritation	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
▪ Eye pain	1 (0.6%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
▪ Foreign body sensation in eyes	0	1 (0.3%)	0	1 (0.2%)
▪ Keratopathy	0	1 (0.3%)	0	1 (0.2%)
▪ Lacrimation increased	0	1 (0.3%)	0	1 (0.2%)
▪ Ocular discomfort	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Ocular hypertension	0	1 (0.3%)	0	1 (0.2%)
▪ Punctate keratitis	0	0	1 (0.6%)	1 (0.2%)
▪ Retinal artery occlusion	0	1 (0.3%)	0	1 (0.2%)
▪ Retinal vascular disorder	0	2 (0.6%)	0	2 (0.4%)

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
▪ Vision blurred	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Visual impairment	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Vitreous detachment	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Vitreous floaters	1 (0.6%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
▪ Vitreous haemorrhage	0	2 (0.6%)	0	2 (0.4%)
▪ Vitritis	0	1 (0.3%)	0	1 (0.2%)
Investigations	4 (2.4%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
▪ IOP increased	4 (2.4%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
General disorders and administration site conditions	0	3 (0.9%)	0	3 (0.6%)
▪ Injection-site irritation	0	1 (0.3%)	0	1 (0.2%)
▪ Injection-site pain	0	2 (0.6%)	0	2 (0.4%)
Injury, poisoning, and procedural complications	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
▪ Corneal abrasion	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Intraocular injection complication	0	1 (0.3%)	0	1 (0.2%)
Fellow eye	5 (3.0%)	7 (2.1%)	5 (3.1%)	12 (2.4%)
Any injection procedure–related non-ocular TEAE	0	2 (0.6%)	1 (0.6%)	3 (0.6%)
Any study conduct–related TEAE	3 (1.8%)	6 (1.8%)	0	6 (1.2%)
Any study conduct–related ocular TEAE	0	2 (0.6%)	0	2 (0.4%)
Study eye	0	2 (0.6%)	0	2 (0.4%)
Fellow eye	0	0	0	0
Any study conduct–related non-ocular TEAE	3 (1.8%)	4 (1.2%)	0	4 (0.8%)
Any TEAE related to aflibercept 2 mg in fellow eye	2 (1.2%)	1 (0.3%)	3 (1.8%)	4 (0.8%)
Any ocular TEAE related to aflibercept 2 mg in fellow eye	2 (1.2%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
Study eye	0	0	0	0
Fellow eye	2 (1.2%)	1 (0.3%)	2 (1.2%)	3 (0.6%)

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
Any non-ocular TEAE related to aflibercept 2 mg in fellow eye	0	0	1 (0.6%)	1 (0.2%)
Any serious pre-treatment AE	0	1 (0.3%)	0	1 (0.2%)
Any serious post-treatment AE	0	2 (0.6%)	3 (1.8%)	5 (1.0%)
Any serious TEAE	36 (21.6%)	65 (19.8%)	29 (17.8%)	94 (19.1%)
Any ocular serious TEAE	5 (3.0%)	6 (1.8%)	2 (1.2%)	8 (1.6%)
Study eye	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Fellow eye	4 (2.4%)	4 (1.2%)	1 (0.6%)	5 (1.0%)
Any non-ocular serious TEAE	32 (19.2%)	61 (18.6%)	27 (16.6%)	88 (17.9%)
Any study drug–related serious TEAE	0	0	0	0
Any injection procedure–related serious TEAE	0	1 (0.3%)	0	1 (0.2%)
Any injection procedure–related ocular serious TEAE	0	1 (0.3%)	0	1 (0.2%)
Study eye	0	1 (0.3%)	0	1 (0.2%)
Fellow eye	0	0	0	0
Any injection procedure–related non-ocular serious TEAE	0	0	0	0
Any study conduct–related serious TEAE	0	0	0	0
Any serious TEAE related to aflibercept 2 mg in fellow eye	0	0	0	0
Any TEAE leading to discontinuation of study drug	3 (1.8%)	9 (2.7%)	2 (1.2%)	11 (2.2%)
Any ocular TEAE leading to discontinuation of study drug	0	2 (0.6%)	0	2 (0.4%)
Study eye	0	2 (0.6%)	0	2 (0.4%)
Fellow eye	0	0	0	0
Any non-ocular TEAE leading to discontinuation of study drug	3 (1.8%)	7 (2.1%)	2 (1.2%)	9 (1.8%)
Any death	5 (3.0%)	9 (2.7%)	4 (2.5%)	13 (2.6%)
Any pre-treatment AE with outcome death	0	0	0	0
Any TEAE with outcome death	5 (3.0%)	8 (2.4%)	3 (1.8%)	11 (2.2%)
Any post-treatment AE with outcome death	0	1 (0.3%)	1 (0.6%)	2 (0.4%)

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
Any treatment-emergent adjudicated APTC event	6 (3.6%)	13 (4.0%)	9 (5.5%)	22 (4.5%)
Any treatment-emergent intraocular inflammation event in study eye	1 (0.6%)	4 (1.2%)	1 (0.6%)	5 (1.0%)
Any treatment-emergent hypertension event	23 (13.8%)	42 (12.8%)	28 (17.2%)	70 (14.3%)
Any treatment-emergent nasal mucosal event	0	0	0	0
Maximum severity (% per treatment group)				
Maximum severity for any ocular TEAE in study eye	49 (29.3%)	118 (36.0%)	56 (34.4%)	174 (35.4%)
Mild severity for any ocular TEAE in study eye	38 (22.8%)	86 (26.2%)	46 (28.2%)	132 (26.9%)
Moderate severity for any ocular TEAE in study eye	10 (6.0%)	30 (9.1%)	9 (5.5%)	39 (7.9%)
Any severe ocular TEAE in study eye	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Maximum severity for any ocular TEAE in fellow eye	52 (31.1%)	91 (27.7%)	52 (31.9%)	143 (29.1%)
Mild severity for any ocular TEAE in fellow eye	37 (22.2%)	69 (21.0%)	36 (22.1%)	105 (21.4%)
Moderate severity for any ocular TEAE in fellow eye	12 (7.2%)	19 (5.8%)	16 (9.8%)	35 (7.1%)
Any severe ocular TEAE in fellow eye	3 (1.8%)	3 (0.9%)	0	3 (0.6%)
Maximum severity for any non-ocular TEAE	96 (57.5%)	195 (59.5%)	104 (63.8%)	299 (60.9%)
Mild severity for any non-ocular TEAE	43 (25.7%)	82 (25.0%)	50 (30.7%)	132 (26.9%)
Moderate severity for any non-ocular TEAE	30 (18.0%)	70 (21.3%)	36 (22.1%)	106 (21.6%)
Any severe non-ocular TEAE	23 (13.8%)	43 (13.1%)	18 (11.0%)	61 (12.4%)
Maximum severity for any ocular serious TEAE in study eye	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Mild severity for any ocular serious TEAE in study eye	0	0	0	0
Moderate severity for any ocular serious TEAE in study eye	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Any severe serious TEAE in study eye	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Maximum severity for any ocular serious TEAE in fellow eye	4 (2.4%)	4 (1.2%)	1 (0.6%)	5 (1.0%)
Mild severity for any ocular serious TEAE in fellow eye	0	1 (0.3%)	0	1 (0.2%)
Moderate severity for any ocular serious TEAE in fellow eye	2 (1.2%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Any severe ocular serious TEAE in fellow eye	2 (1.2%)	1 (0.3%)	0	1 (0.2%)

Safety analysis set	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
Maximum severity for any non-ocular serious TEAE	32 (19.2%)	61 (18.6%)	27 (16.6%)	88 (17.9%)
Mild severity for any non-ocular serious TEAE	2 (1.2%)	2 (0.6%)	0	2 (0.4%)
Moderate severity for any non-ocular serious TEAE	9 (5.4%)	18 (5.5%)	9 (5.5%)	27 (5.5%)
Any severe non-ocular serious TEAE	21 (12.6%)	41 (12.5%)	18 (11.0%)	59 (12.0%)

AE=adverse event; APTC=Antiplatelet Trialists' Collaboration; IOP=intraocular pressure; MedDRA=Medical Dictionary for Regulatory Activities; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; TEAE=treatment-emergent adverse event.

[a]A pre-treatment AE was an AE starting from signing the informed consent form to before the first dose of study drug.

[b]A TEAE was an AE starting after the first dose of study drug to the last dose of study drug (active or sham) plus 30 days. Additionally, for patients who were still participating in the study (i.e., had not been withdrawn) as of the week 60 visit all AEs up through the date of the last visit were to be considered treatment-emergent.

[c]A post-treatment AE was an AE starting after the end of the on-treatment (TEAE) period.

[d]Ocular study drug–related TEAEs (Preferred Term MedDRA Version 25.0) in the study eye by primary system organ class and preferred term through week 60.

[e]Ocular TEAEs (Preferred Term MedDRA Version 25.0) in the study eye by primary system organ class and preferred term occurring in ≥1.0% of patients in any treatment group through week 60.

Source: PHOTON Clinical Study Report (week 60).

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

Primary system organ class Preferred term MedDRA version 25.0	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
Ocular TESAEs in study eye				
Ulcerative keratitis	1 (0.6%)	0	0	0
Cataract subcapsular	0	1 (0.3%)	0	0
Intraocular pressure increased	0	1 (0.3%)	0	0
Retinal detachment	0	0	1 (0.6%)	0
Vitreous haemorrhage	0	0	1 (0.6%)	0
Non-ocular TESAEs reported in ≥2 patients				
Number of patients with at least 1 such AE	32 (19.2%)	61 (18.6%)	27 (16.6%)	88 (17.9%)
▪ Blood and lymphatic system disorders	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Anaemia	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Cardiac disorders	9 (5.4%)	20 (6.1%)	7 (4.3%)	27 (5.5%)
▪ Acute left ventricular failure	3 (1.8%)	2 (0.6%)	0	2 (0.4%)
▪ Acute myocardial infarction	2 (1.2%)	5 (1.5%)	2 (1.2%)	7 (1.4%)
▪ Cardiac arrest	2 (1.2%)	3 (0.9%)	0	3 (0.6%)
▪ Cardiac failure	1 (0.6%)	2 (0.6%)	0	2 (0.4%)
▪ Coronary artery disease	1 (0.6%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
▪ Coronary artery occlusion	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
▪ Coronary artery stenosis	0	2 (0.6%)	0	2 (0.4%)
▪ Myocardial infarction	2 (1.2%)	4 (1.2%)	3 (1.8%)	7 (1.4%)
General disorders and administration-site conditions	3 (1.8%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
▪ Chest pain	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Infections and infestations	11 (6.6%)	14 (4.3%)	2 (1.2%)	16 (3.3%)
▪ COVID-19	0	3 (0.9%)	1 (0.6%)	4 (0.8%)
▪ COVID-19 pneumonia	2 (1.2%)	3 (0.9%)	0	3 (0.6%)
▪ Cellulitis	2 (1.2%)	0	1 (0.6%)	1 (0.2%)
▪ Gangrene	2 (1.2%)	0	0	0
▪ Pneumonia	1 (0.6%)	4 (1.2%)	0	4 (0.8%)
▪ Sepsis	2 (1.2%)	0	0	0
Metabolism and nutrition disorders	5 (3.0%)	3 (0.9%)	4 (2.5%)	7 (1.4%)
▪ Hyperkalaemia	0	0	2 (1.2%)	2 (0.4%)
▪ Hypoglycaemia	0	2 (0.6%)	1 (0.6%)	3 (0.6%)
▪ Hyponatraemia	2 (1.2%)	0	0	0

Primary system organ class Preferred term MedDRA version 25.0	Aflibercept 2 mg Q8W N=167	Aflibercept 8 mg Q12W N=328	Aflibercept 8 mg Q16W N=163	Aflibercept 8 mg Pooled N=491
Musculoskeletal and connective tissue disorders	1 (0.6%)	3 (0.9%)	3 (1.8%)	6 (1.2%)
▪ Neuropathic arthropathy	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Nervous system disorders	2 (1.2%)	5 (1.5%)	6 (3.7%)	11 (2.2%)
▪ Cerebrovascular accident	0	2 (0.6%)	3 (1.8%)	5 (1.0%)
▪ Transient ischaemic attack	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Renal and urinary disorders	2 (1.2%)	9 (2.7%)	2 (1.2%)	11 (2.2%)
▪ Acute kidney injury	2 (1.2%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
Respiratory, thoracic, and mediastinal disorders	3 (1.8%)	5 (1.5%)	2 (1.2%)	7 (1.4%)
▪ Acute respiratory failure	2 (1.2%)	1 (0.3%)	2 (1.2%)	3 (0.6%)
▪ Pulmonary embolism	0	2 (0.6%)	0	2 (0.4%)

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.

Source: PHOTON Clinical Study Report (week 60).

PHOTON study: 96-week safety results 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 and Table 22 which shows similar safety data across 2 mg and 8 mg aflibercept.

Table 21 Intraocular inflammation for week 96

	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Any treatment emergent intraocular inflammation	2 (1.2%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
Any treatment emergent hypertension event	27 (16.2%)	51 (15.5%)	34 (20.9%)	85 (17.3%)
Any treatment emergent oral mucosal event	0	1 (0.3%)	0	(0.2%)

Table 22 PHOTON study: 96-week safety results (ocular/non-ocular TESAE)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Number of Patients with at Least One Such AE of study eye, n (%)	2 (1.2%)	3 (0.9%)	3 (1.8%)	6 (1.2%)
Eye disorders	**2 (1.2%)**	**2 (0.6%)**	**3 (1.8%)**	**5 (1.0%)**
• Cataract	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
• Cataract nuclear	0	1 (0.3%)	0	1 (0.2%)
• Cataract subcapsular	0	1 (0.3%)	0	1 (0.2%)
• Retinal detachment	0	0	1 (0.6%)	1 (0.2%)
• Retinal neovascularisation	0	0	1 (0.6%)	1 (0.2%)
• Ulcerative keratitis	1 (0.6%)	0	0	0
• Vitreous haemorrhage	0	0	2 (1.2%)	2 (0.4%)
Investigations	**0**	**1 (0.3%)**	**0**	**1 (0.2%)**
• Intraocular pressure increased	0	1 (0.3%)	0	1 (0.2%)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Number of Patients with at Least One Such AE of fellow eye, n (%)	4 (2.4%)	7 (2.1%)	2 (1.2%)	9 (1.8%)
Eye disorders	4 (2.4%)	6 (1.8%)	2 (1.2%)	8 (1.6%)
Cataract	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Diabetic retinopathy	1 (0.6%)	3 (0.9%)	0	3 (0.6%)

Epiretinal membrane	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Retinal artery occlusion	1 (0.6%)	0	0	0
Retinal haemorrhage	0	1 (0.3%)	0	1 (0.2%)
Tractional retinal detachment	0	0	1 (0.6%)	1 (0.2%)
Vitreous haemorrhage	2 (1.2%)	1 (0.3%)	0	1 (0.2%)
Investigations	0	1 (0.3%)	0	1 (0.2%)
Intraocular pressure increased	0	1 (0.3%)	0	1 (0.2%)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Number of Patients with at Least One Such AE, n (%)	42 (25.1%)	75 (22.9%)	39 (23.9%)	114 (23.2%)
Blood and lymphatic system disorders	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Anaemia	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Cardiac disorders	13 (7.8%)	26 (7.9%)	9 (5.5%)	35 (7.1%)
Acute left ventricular failure	3 (1.8%)	2 (0.6%)	0	2 (0.4%)
Acute myocardial infarction	2 (1.2%)	10 (3.0%)	2 (1.2%)	12 (2.4%)
Angina pectoris	0	1 (0.3%)	0	1 (0.2%)
Angina unstable	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Arteriosclerosis coronary artery	1 (0.6%)	0	0	0
Atrial flutter	0	0	1 (0.6%)	1 (0.2%)
Atrioventricular block	0	1 (0.3%)	0	1 (0.2%)
Atrioventricular block second degree	1 (0.6%)	0	0	0
Cardiac arrest	3 (1.8%)	3 (0.9%)	0	3 (0.6%)
Cardiac failure	1 (0.6%)	2 (0.6%)	0	2 (0.4%)
Cardiac failure acute	0	0	1 (0.6%)	1 (0.2%)
Cardiac failure congestive	1 (0.6%)	0	0	0
Coronary artery disease	2 (1.2%)	3 (0.9%)	2 (1.2%)	5 (1.0%)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Cardiac disorders				
Coronary artery occlusion	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Coronary artery stenosis	0	3 (0.9%)	0	3 (0.6%)
Left ventricular failure	0	0	1 (0.6%)	1 (0.2%)
Myocardial infarction	3 (1.8%)	5 (1.5%)	3 (1.8%)	8 (1.6%)

Supraventricular tachycardia	1 (0.6%)	0	0	0
Ventricular extrasystoles	0	0	1 (0.6%)	1 (0.2%)
Ventricular tachycardia	1 (0.6%)	0	0	0
Ear and labyrinth disorders	0	1 (0.3%)	0	1 (0.2%)
Vertigo	0	1 (0.3%)	0	1 (0.2%)
Gastrointestinal disorders	2 (1.2%)	1 (0.3%)	4 (2.5%)	5 (1.0%)
Ileus	0	0	1 (0.6%)	1 (0.2%)
Impaired gastric emptying	0	0	1 (0.6%)	1 (0.2%)
Inguinal hernia	0	0	1 (0.6%)	1 (0.2%)
Intestinal obstruction	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Intra-abdominal fluid collection	1 (0.6%)	0	0	0
Peptic ulcer	0	0	1 (0.6%)	1 (0.2%)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Gastrointestinal disorders				
Pneumoperitoneum	1 (0.6%)	0	0	0
Vomiting	0	0	1 (0.6%)	1 (0.2%)
General disorders and administration site conditions	3 (1.8%)	4 (1.2%)	3 (1.8%)	7 (1.4%)
Asthenia	0	0	1 (0.6%)	1 (0.2%)
Chest pain	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Death	1 (0.6%)	2 (0.6%)	0	2 (0.4%)
Oedema peripheral	1 (0.6%)	0	0	0
Sudden death	0	0	1 (0.6%)	1 (0.2%)
Hepatobiliary disorders	2 (1.2%)	0	2 (1.2%)	2 (0.4%)
Bile duct stone	1 (0.6%)	0	0	0
Cholecystitis	1 (0.6%)	0	0	0
Cholecystitis acute	0	0	1 (0.6%)	1 (0.2%)
Cholelithiasis	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
Infections and infestations	14 (8.4%)	22 (6.7%)	6 (3.7%)	28 (5.7%)
Bronchitis	0	1 (0.3%)	0	1 (0.2%)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)

Musculoskeletal and connective tissue disorders	1 (0.6%)	4 (1.2%)	3 (1.8%)	7 (1.4%)
Arthritis	0	1 (0.3%)	0	1 (0.2%)
Exostosis	0	1 (0.3%)	0	1 (0.2%)
Intervertebral disc protrusion	1 (0.6%)	0	0	0
Neuropathic arthropathy	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Osteoarthritis	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Rotator cuff syndrome	0	0	1 (0.6%)	1 (0.2%)
Spondylolisthesis	0	0	1 (0.6%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.2%)	9 (2.7%)	4 (2.5%)	13 (2.6%)
Breast cancer	0	1 (0.3%)	0	1 (0.2%)
Colon cancer	0	1 (0.3%)	0	1 (0.2%)
Colon cancer metastatic	0	0	1 (0.6%)	1 (0.2%)
Endometrial cancer	0	1 (0.3%)	0	1 (0.2%)
Gastric cancer	0	0	1 (0.6%)	1 (0.2%)
Gastrointestinal neoplasm	0	0	1 (0.6%)	1 (0.2%)
Hepatic cancer	1 (0.6%)	0	0	0
Hepatic cancer metastatic	0	0	1 (0.6%)	1 (0.2%)
Invasive breast carcinoma	0	0	1 (0.6%)	1 (0.2%)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Musculoskeletal and connective tissue disorders	1 (0.6%)	4 (1.2%)	3 (1.8%)	7 (1.4%)
Arthritis	0	1 (0.3%)	0	1 (0.2%)
Exostosis	0	1 (0.3%)	0	1 (0.2%)
Intervertebral disc protrusion	1 (0.6%)	0	0	0
Neuropathic arthropathy	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Osteoarthritis	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Rotator cuff syndrome	0	0	1 (0.6%)	1 (0.2%)
Spondylolisthesis	0	0	1 (0.6%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.2%)	9 (2.7%)	4 (2.5%)	13 (2.6%)
Breast cancer	0	1 (0.3%)	0	1 (0.2%)
Colon cancer	0	1 (0.3%)	0	1 (0.2%)
Colon cancer metastatic	0	0	1 (0.6%)	1 (0.2%)
Endometrial cancer	0	1 (0.3%)	0	1 (0.2%)

Gastric cancer	0	0	1 (0.6%)	1 (0.2%)
Gastrointestinal neoplasm	0	0	1 (0.6%)	1 (0.2%)
Hepatic cancer	1 (0.6%)	0	0	0
Hepatic cancer metastatic	0	0	1 (0.6%)	1 (0.2%)
Invasive breast carcinoma	0	0	1 (0.6%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	1 (0.6%)	4 (1.2%)	3 (1.8%)	7 (1.4%)
Arthritis	0	1 (0.3%)	0	1 (0.2%)
Exostosis	0	1 (0.3%)	0	1 (0.2%)
Intervertebral disc protrusion	1 (0.6%)	0	0	0
Neuropathic arthropathy	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Osteoarthritis	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Rotator cuff syndrome	0	0	1 (0.6%)	1 (0.2%)
Spondylolisthesis	0	0	1 (0.6%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.2%)	9 (2.7%)	4 (2.5%)	13 (2.6%)
Breast cancer	0	1 (0.3%)	0	1 (0.2%)
Colon cancer	0	1 (0.3%)	0	1 (0.2%)
Colon cancer metastatic	0	0	1 (0.6%)	1 (0.2%)
Endometrial cancer	0	1 (0.3%)	0	1 (0.2%)
Gastric cancer	0	0	1 (0.6%)	1 (0.2%)
Gastrointestinal neoplasm	0	0	1 (0.6%)	1 (0.2%)
Hepatic cancer	1 (0.6%)	0	0	0
Hepatic cancer metastatic	0	0	1 (0.6%)	1 (0.2%)
Invasive breast carcinoma	0	0	1 (0.6%)	1 (0.2%)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Nervous system disorders				
Loss of consciousness	0	1 (0.3%)	0	1 (0.2%)
Metabolic encephalopathy	0	0	1 (0.6%)	1 (0.2%)
Presyncope	0	0	1 (0.6%)	1 (0.2%)
Seizure	1 (0.6%)	0	0	0
Subarachnoid haemorrhage	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Syncope	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Thalamus haemorrhage	0	1 (0.3%)	0	1 (0.2%)
Transient ischaemic attack	0	1 (0.3%)	1 (0.6%)	2 (0.4%)

Psychiatric disorders	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Mental status changes	1 (0.6%)	0	0	0
Stress	0	1 (0.3%)	0	1 (0.2%)
Renal and urinary disorders	3 (1.8%)	13 (4.0%)	4 (2.5%)	17 (3.5%)
Acute kidney injury	2 (1.2%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
Azotaemia	0	1 (0.3%)	0	1 (0.2%)
Chronic kidney disease	0	1 (0.3%)	0	1 (0.2%)
Diabetic nephropathy	0	1 (0.3%)	0	1 (0.2%)

Table 23 PHOTON study: 96-week safety results (ocular/non-ocular TESAE) (Continued)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Infections and infestations				
Sepsis	4 (2.4%)	2 (0.6%)	0	2 (0.4%)
Septic shock	0	1 (0.3%)	0	1 (0.2%)
Urosepsis	1 (0.6%)	0	0	0
Wound infection staphylococcal	0	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	7 (4.2%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
Alcohol poisoning	0	0	1 (0.6%)	1 (0.2%)
Ankle fracture	0	1 (0.3%)	0	1 (0.2%)
Fall	0	1 (0.3%)	0	1 (0.2%)
Femoral neck fracture	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
Head injury	0	1 (0.3%)	0	1 (0.2%)
Hip fracture	2 (1.2%)	0	0	0
Humerus fracture	1 (0.6%)	0	0	0
Lower limb fracture	1 (0.6%)	0	0	0
Post procedural haemorrhage	0	1 (0.3%)	0	1 (0.2%)
Rib fracture	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Road traffic accident	1 (0.6%)	0	0	0
Subdural haematoma	1 (0.6%)	0	0	0

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Injury, poisoning and procedural complications				

Traumatic intracranial haemorrhage	1 (0.6%)	0	0	0
Upper limb fracture	1 (0.6%)	0	0	0
Vascular pseudoaneurysm	1 (0.6%)	0	0	0
Investigations	0	1 (0.3%)	0	1 (0.2%)
Blood glucose increased	0	1 (0.3%)	0	1 (0.2%)
Metabolism and nutrition disorders	6 (3.6%)	3 (0.9%)	5 (3.1%)	8 (1.6%)
Diabetes mellitus	1 (0.6%)	0	0	0
Diabetic ketoacidosis	1 (0.6%)	0	0	0
Diabetic metabolic decompensation	1 (0.6%)	0	0	0
Hyperkalaemia	1 (0.6%)	0	3 (1.8%)	3 (0.6%)
Hypoglycaemia	0	2 (0.6%)	2 (1.2%)	4 (0.8%)
Hyponatraemia	2 (1.2%)	0	0	0
Ketoacidosis	0	0	1 (0.6%)	1 (0.2%)
Type 1 diabetes mellitus	0	0	1 (0.6%)	1 (0.2%)
Type 2 diabetes mellitus	0	1 (0.3%)	0	1 (0.2%)
Nervous system disorders				
Loss of consciousness	0	1 (0.3%)	0	1 (0.2%)
Metabolic encephalopathy	0	0	1 (0.6%)	1 (0.2%)
Presyncope	0	0	1 (0.6%)	1 (0.2%)
Seizure	1 (0.6%)	0	0	0
Subarachnoid haemorrhage	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Syncope	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Thalamus haemorrhage	0	1 (0.3%)	0	1 (0.2%)
Transient ischaemic attack	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
Psychiatric disorders	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Mental status changes	1 (0.6%)	0	0	0
Stress	0	1 (0.3%)	0	1 (0.2%)
Renal and urinary disorders	3 (1.8%)	13 (4.0%)	4 (2.5%)	17 (3.5%)
Acute kidney injury	2 (1.2%)	7 (2.1%)	1 (0.6%)	8 (1.6%)
Azotaemia	0	1 (0.3%)	0	1 (0.2%)
Chronic kidney disease	0	1 (0.3%)	0	1 (0.2%)
Diabetic nephropathy	0	1 (0.3%)	0	1 (0.2%)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Renal and urinary disorders				
End stage renal disease	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Nephrotic syndrome	0	0	1 (0.6%)	1 (0.2%)
Renal failure	0	2 (0.6%)	1 (0.6%)	3 (0.6%)
Ureterolithiasis	1 (0.6%)	0	0	0
Reproductive system and breast disorders	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
Prostatitis	1 (0.6%)	0	0	0
Scrotal oedema	0	0	1 (0.6%)	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	3 (1.8%)	8 (2.4%)	3 (1.8%)	11 (2.2%)
Acute respiratory failure	2 (1.2%)	2 (0.6%)	2 (1.2%)	4 (0.8%)
Aspiration	0	1 (0.3%)	0	1 (0.2%)
Chronic obstructive pulmonary disease	0	1 (0.3%)	0	1 (0.2%)
Dyspnoea	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Haemoptysis	0	1 (0.3%)	0	1 (0.2%)
Hypoxia	0	1 (0.3%)	0	1 (0.2%)
Pulmonary embolism	0	2 (0.6%)	1 (0.6%)	3 (0.6%)
Pulmonary fibrosis	0	0	1 (0.6%)	1 (0.2%)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Vascular disorders				
Hypertensive urgency	0	0	1 (0.6%)	1 (0.2%)
Hypotension	1 (0.6%)	0	2 (1.2%)	2 (0.4%)
Orthostatic hypotension	1 (0.6%)	0	0	0
Peripheral vascular disorder	0	1 (0.3%)	0	1 (0.2%)
Peripheral venous disease	0	0	1 (0.6%)	1 (0.2%)
Thrombosis	0	0	1 (0.6%)	1 (0.2%)

Primary System Organ Class Preferred Term	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Respiratory, thoracic and mediastinal disorders				
Pulmonary oedema	0	1 (0.3%)	0	1 (0.2%)

Respiratory distress	0	2 (0.6%)	0	2 (0.4%)
Respiratory failure	1 (0.6%)	0	0	0
Skin and subcutaneous tissue disorders	0	3 (0.9%)	1 (0.6%)	4 (0.8%)
Diabetic foot	0	2 (0.6%)	1 (0.6%)	3 (0.6%)
Skin ulcer	0	1 (0.3%)	0	1 (0.2%)
Surgical and medical procedures	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Skin neoplasm excision	1 (0.6%)	0	0	0
Thrombosis prophylaxis	0	1 (0.3%)	0	1 (0.2%)
Vascular disorders	3 (1.8%)	7 (2.1%)	6 (3.7%)	13 (2.6%)
Aortic stenosis	0	2 (0.6%)	0	2 (0.4%)
Arteriosclerosis	0	1 (0.3%)	0	1 (0.2%)
Haematoma	0	1 (0.3%)	0	1 (0.2%)
Hypertension	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Hypertensive emergency	1 (0.6%)	1 (0.3%)	0	1 (0.2%)

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

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

6. References

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Appendix A. Main characteristics of studies included

Tabel 1 Main characteristic of studies included

Trial name: PHOTON	**NCT number: NCT04429503**
Objective	The primary objective of the study is 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 a non-inferior BCVA change compared with aflibercept 2 mg every 8 weeks (after 5 initial injections at 4-week intervals) in participants with DME.
Publications – title, author, journal, year	Submitted for publication
Study type and design	PHOTON is an ongoing phase 2/3, multicentre, randomised, double-masked study in participants with DME involving the centre of the macula that investigates the efficacy, safety, and tolerability of intravitreal administration of aflibercept 8 mg compared with aflibercept 2 mg. The primary objective of the study is 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 a non-inferior BCVA change compared with aflibercept 2 mg every 8 weeks (after 5 initial injections at 4-week intervals) in participants with DME. The secondary objectives are to determine the effect of aflibercept 8 mg versus aflibercept 2 mg on anatomic and other visual measures of response, 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/baseline period, a 92-week treatment period, and an end-of-study visit at week 96. The optional open-label extension phase will include an additional 60 weeks of treatment with aflibercept 8 mg, with an end-of-study visit at week 156, for which exploratory analyses will be reported separately. The study is being conducted at 138 centres in Canada, Czech Republic, Germany, Hungary, Japan, the United Kingdom, and the United States. Participants were randomly assigned in a 1:2:1 ratio to 1 of 3 parallel treatment groups:

- Aflibercept 2 mg administered Q8W and at 4-week intervals after the 5 initial injections as indicated in the label (100)
- Aflibercept 8 mg administered Q12W and at 4-week intervals after the 3 initial injections
- Aflibercept 8 mg administered Q16W and at 4-week intervals after the 3 initial injections

Randomisation was stratified based on the baseline CRT (<400 µm, ≥400 µm), prior DME treatment (yes, no), and geographical region (Rest of world, Japan), to ensure a balanced distribution of the treatment groups within each stratum.

The study uses a double-masked design. To preserve masking, sham injections were performed in all participants at treatment visits in which participants did not receive an active injection. Fellow-eye treatment was allowed with aflibercept 2 mg at the investigator's discretion for indications approved by the governing authorities. The treated fellow-eye was not considered as an additional study eye.

Assessments for dose regimen modifications (DRMs) were performed in all participants treated with aflibercept 8 mg, at all visits beginning at week 16 (after 3 monthly loading doses). Based on these assessments, participants in the aflibercept 8 mg group 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 greater than Q8W. Participants in the aflibercept 2 mg group remained on the fixed Q8W dosing throughout the study.

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

- A participant in the aflibercept 8 mg Q12W or Q16W group who met the DRM criteria at week 16 or week 20 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 did not meet the DRM criteria at week 16 or week 20 and who met the 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 the 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 by 4 weeks) based on the pre-specified DRM criteria.

DRM criteria in the PHOTON study

Dosing interval[a]	Study period	DRM criteria
Shortened dosing interval[b]	Baseline to week 96	**1.** >10-letter loss in BCVA from week 12 in association with persistent or worsening DME AND **2.** >50-µm increase in CRT from week 12
Extended dosing interval[c]	Week 52 to week 96	**1.** <5-letter loss in BCVA from week 12 AND **2.** CRT <300 µm for Cirrus SD-OCT (or <320 µm on Spectralis SD-OCT)

BCVA=best corrected visual acuity; CRT=central retinal thickness; DME=diabetic macular oedema; DRM=dose regimen modification; SD-OCT=spectral-domain optical coherence tomography.

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

[b]Dosing interval was shortened if both DRM criteria were met. The change in CRT for these criteria was assessed at the site.

[c]Interval extension if both the abovementioned DRM criteria were met at visits with active injection.

Source: PHOTON Clinical Study Protocol.

Sample size (n)	660
Main inclusion criteria	○ Diabetic macular edema (DME) with central involvement in the study eye ○ Best corrected visual acuity (BCVA) early treatment diabetic retinopathy study (ETDRS) letter score of 78 to 24 (approximate Snellen equivalent of 20/32 to 20/320) in the study eye with decreased vision determined to be primarily the result of DME

Trial name: PHOTON		NCT number: NCT04429503
	○ Willing and able to comply with clinic visits and study-related procedures ○ Provide informed consent signed by study participant or legally acceptable representative	
Main exclusion criteria	○ Evidence of macular edema due to any cause other than diabetes mellitus in either eye ○ Active proliferative diabetic retinopathy in the study eye ○ IVT anti-VEGF treatment (aflibercept, ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) or panretinal laser photocoagulation (PRP) /macular laser photocoagulation within 12 weeks (84 days) or intraocular or periocular corticosteroids within 16 weeks (112 days) of the screening visit in the study eye ○ Prior IVT investigational agents in either eye (eg, anti-ang-2/anti-VEGF bispecific monoclonal antibodies, gene therapy, etc.) at any time ○ Treatment with ocriplasmin (JETREA®) in the study eye at any time	
Intervention	Aflibercept 8 mg administered every 12 weeks (Q12W), after 3 initial injections at 4-week intervals (n=329) Aflibercept 8 mg administered every 16 weeks (Q16W), after 3 initial injections at 4-week intervals (n=164)	
Comparator(s)	Aflibercept 2 mg administered every 8 weeks (Q8W), after 5 initial injections at 4-week intervals (n=167)	
Follow-up time	At week 48, 60, 96 and 156	
Primary, secondary and exploratory endpoints	**Primary endpoint**	• Change from baseline in BCVA measured by the ETDRS letter score at week 48
	Key secondary efficacy endpoints; hierarchised criteria	• Change from baseline in BCVA measured by the ETDRS letter score at week 60 (EP-SAP only) • Proportion of participants with ≥2-step improvement in the DRSS score at week 48
	Secondary safety endpoint	• Safety evaluation by assessment of AEs and SAEs through weeks 48, 60, 96, and 156
	Additional secondary efficacy endpoints	• Proportion of participants gaining at least 15 letters in the BCVA from baseline at week 48 • Proportion of participants achieving an ETDRS letter score of at least 69 at week 48 • Proportion of participants without fluid (defined as no IRF and no SRF) at the foveal centre at week 48

Trial name: PHOTON		NCT number: NCT04429503
		• Change from baseline in CRT at week 48 • Proportion of patients without leakage on FA at week 48 • Change from baseline in the NEI-VFQ-25 total score at week 48
	Exploratory efficacy endpoints [reported in week 48 and week 60]	• Proportion of patients without retinal fluid (total fluid, IRF and/or SRF) at the foveal centre and in the centre subfield at week 48 and week 96 • Time to fluid-free retina over 48 weeks and 96 weeks (total fluid, IRF, and/or SRF at foveal centre and in the centre subfield) • Proportion of patients with sustained fluid-free retina over 48 weeks and 96 weeks (total fluid, IRF, and/or SRF at foveal centre and in the centre subfield) • Proportion of patients without CSME at week 48 and week 96 • Proportion of patients with a ≥3-step improvement in the DRSS score at week 48 and week 96 • Change from baseline in BCVA averaged over the period from week 36 to week 48 • Change from baseline in BCVA averaged over the period from week 48 to week 60 • Proportions of patients gaining and losing ≥5 or ≥10 letters at week 48 and week 96 • Proportion of patients losing ≥15 letters at week 48 and week 96 • Proportion of patients randomised to aflibercept 8 mg Q16W maintaining Q16W dosing interval or longer through weeks 48, 60, and 96 • Proportion of patients randomised to aflibercept 8 mg Q12W maintaining Q12W dosing interval or longer through weeks 48, 60 and 96 • Proportion of patients with an assigned injection interval of ≥ 16 or ≥ 20 weeks based on assessment at the last injection visit
	Endpoints included in this application:	

Trial name: PHOTON	NCT number: NCT04429503
	Change from baseline in BCVA measured by the ETDRS letter score at week 48 and 60. Proportion of patients losing ≥15 letters at week 48 and week 96 Change from baseline in CRT at week 48 Change from baseline in the NEI-VFQ-25 total score at week 48 Safety evaluation by assessment of AEs and SAEs through weeks 48, 60 and 96.
Method of analysis	All efficacy analyses were conducted using the full analysis set (FAS) population. In addition, the change from baseline in BCVA at week 48 and week 60 was analysed using the per protocol set (PPS) population as a supplementary analysis. Treatment compliance/ administration and all clinical safety variables were analysed using the safety analysis set (SAF). • The FAS included all randomised participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomised). The FAS is the primary analysis set for efficacy endpoints • The PPS included all participants in the FAS who had a baseline and at least 1 post-baseline assessment of BCVA and did not have any relevant important protocol violations that affect the primary efficacy variable • The SAF included all randomised participants who received any study treatment; it was based on the treatment received (as treated) The primary analysis is based on the estimand concept. The estimand of primary interest will be based mainly on a hypothetical strategy. It describes the change from baseline for all patients who started treatment, assuming all patients 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: • Population: Defined by the inclusion/exclusion criteria. All efficacy analyses will be conducted using the FAS.

	• Variable: Change from baseline to week 48 in BCVA • Treatment condition: Intention to treat with HD aflibercept administered every 12 weeks (HDq12) after 3 initial monthly injections or every 16 weeks (HDq16) after 3 initial monthly injections each versus aflibercept 2 mg administered every 8 weeks (2q8) after 5 initial monthly injections; dose regimen modifications do not affect patient's assigned ITT regimen. • Intercurrent events: Premature discontinuation from treatment; missed injections; use of prohibited medication; wrong study intervention administered. • Population-level summary: Difference in least-square (LS) mean change from baseline to week 48 in BCVA between HDq12 and 2q8 (and HDq16 and 2q8) resulting from a mixed-model for repeated measurements (MMRM).
Subgroup analyses	Subgroups for efficacy analyses were: • Sex: male, female • Age at enrollment: <55 years, ≥55 years to <65 years, ≥65 years to < 75 years, ≥75 years • Race (only subgroups with sufficient sample size): White, Black or African American, Asian • Ethnicity: Not Hispanic or Latino, Hispanic or Latino • Baseline BCVA (≤73 letters, >73 letters) • Geographic region: Japan, Rest of the world • Baseline CRT category (<400 µm, ≥400 µm) • Prior DME treatment (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.
Other relevant information	Not applicable

Appendix B. Efficacy results per study

Results per study

Tabel 2 Results per study

Results of PHOTON - NCT04429503											
				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 (least square mean) in BCVA measured by ETDRS score from baseline to.										The primary analysis is based on the estimand concept. The estimand of primary interest will be based mainly on a hypothetical strategy. It describes the change from baseline for all patients who started treatment, assuming all patients 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:	
Week 48:											
	2q8	167	8.67 (7.2, 10.1)								
	8q12	328	8.10 (6.9, 9.3)	-0.57	-2.26 - 1.13	<0.0001					
	8q16	163	7.23 (5.8, 8.6)	-1.44	-3.27 - 0.39	0.0031					
Week 60:											
	2q8	167	9.40 (7.9, 10.9)								
	8q12	328	8.52 (7.3, 9.8)	-0.88	-2.67-0.91	0.0003					
	8q16	163	7.64 (6.2, 9.1)	-1.76	-3.71-0.19	0.0122					

Results of PHOTON - NCT04429503											
				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:										• Population: Defined by the inclusion/exclusion criteria. All efficacy analyses will be conducted using the FAS. • Variable: Change from baseline to week 48 in BCVA • Treatment condition: Intention to treat with HD aflibercept administered every 12 weeks (HDq12) after 3 initial monthly injections or every 16 weeks (HDq16) after 3 initial monthly injections each versus aflibercept 2 mg administered every 8 weeks (2q8) after 5 initial monthly injections; dose regimen modifications do not affect patient's assigned ITT regimen. • Intercurrent events: Premature discontinuation from treatment; missed injections; use of prohibited	
	2q8	167	7.70 (6.0, 9.4)								
	8q12	328	8.15 (6.9, 9.4)	0.45	-1.55-2.45	<0.0001					
	8q16	163	6.59 (5.1, 8.1)	-1.11	-3.27-1.05	0.0044					

Results of PHOTON - NCT04429503											
				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		
										medication; wrong study intervention administered. • Population-level summary: Difference in least-square (LS) mean change from baseline to week 48 in BCVA between HDq12 and 2q8 (and HDq16 and 2q8) resulting from a mixed-model for repeated measurements (MMRM). The following 2 hypotheses will be tested in the primary analysis: • HDq12 is non-inferior to 2q8 regarding the mean change in BCVA from baseline to week 48 using a non-inferiority margin of 4 letters. • HDq16 is non-inferior to 2q8 regarding the mean change in BCVA from baseline	

Results of PHOTON - NCT04429503											
				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		
										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 (HDq16 vs. 2q8 and HDq12 vs. 2q8) and baseline CRT category (<400 µm, ≥400 µm), prior DME treatment (yes, no), geographical region (Rest of world, Japan), and visit as fixed effects as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.	
Proportion of patient losing less than 15 ETDRS letters at:	2q8	165								Proportion of participants losing less than 15 letters in BCVA from baseline summarized descriptively by treatment group for all	

Results of PHOTON - NCT04429503												
				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 48	8q12	326	163 (98.8 %) (95.7-99.9%)	-0.9%	-3.38-2.32%		0.99	0.97-1.01		observed cases until the occurrence of an ICE with imputation of missing values with LOCF in the FAS population. (Missing data were not included in the denominator)	
	8q16	163	319 (97.9 %) (95.6-99.1%)	0.6%	-2.29-3.77%		1.01	0.99-1.03			
Week 60	2q8	165	162 (99.4 %) (96.6-99.98%)								
	8q12	326	164 (99.4 %) (96.7-99.98%)	-1.5%	3.87-1.33%		0.98	0.97-1.00			
	8q16	163	319 (97.9 %) (95.6-99.1%)	-0.0%	-2.84-2.80%		0.99	0.98-1.02			
Week 96	2q8	165	162 (99.4 %) (96.6-99.98%)								
	8q12	326	159 (96.4 %) (92.3-98.7%)	0.3%				0.97-1.04			

Results of PHOTON - NCT04429503											
				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		
					-3.00-4.60%		1.00				
	8q16	163	315 (96.6 %) (94.0-98.3%)	2.4%				0.99-1.06			
							1.02				
			161 (98.8 %)		-1.17-6.64%						
			(95.6-99.9%)								
Change from baseline in central retinal thickness at:										A mixed model for repeated measurements (MMRM) was used with baseline CRT measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline	
Week 48:	2q8	167	-164.8 (-182.2, -147.5)								
	8q12	328	-176.8 (-188.0, -165.5)	-11.92	-30.3, 6.47	0.2028					
	8q16	163	-148.8 (-167.5, -130.2)	16.01	-7.53, 39.5	0.1817					
Week 60:	2q8	167	-194.2 (-208.2, -180.2)								

Results of PHOTON - NCT04429503											
				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		
	8q12	328	-181.0 (-193.9, -170.0)	12.2	-3.74, 28.2	0.1332				and visit and the interaction between treatment and visit.	
	8q16	163	-166.3 (-183.0, -149.5)	27.9	8.06, 47.7	0.0060					
Week 96:	2q8	167	-191.3 (-209.1, -173.4)							Intercurrent events (ICE) were handled according to Table 1 of SAP. p-value for the two-sided superiority test.	
	8q12	328	-194.0 (-205.9, -182.1)	-2.72	-23.05, 17.61	0.7925					
	8q16	163	-158.4 (-177.4, -139.5)	32.87	7.79, 57.95	0.0104					
Change from baseline in NEI-VFQ total score at Week 48	2q8	167	2.82 (0.66, 4.98)							A mixed model for repeated measurements (MMRM) was used with baseline NEI-VFQ-25 total score measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [=400µm], prior treatment for DME (per EDC) [yes vs. no]) as	
	8q12	328	4.06 (2.49, 5.63)	1.25	-1.09 - 3.58	0.2941					
	8q16	163	2.94 (1.12, 4.76)	0.13	-2.37 - 2.62	0.9208					

Results of PHOTON - NCT04429503											
				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		
										fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error. Intercurrent events (ICE) were handled according to Table 1 of SAP. p-value for the two-sided superiority test	
Any treatment-emergent intraocular inflammation event 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:	2q8	167	1 (0.6 %) (0.02-3.29%)								

Results of PHOTON - NCT04429503											
				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		
	8q12	328	4 (1.2 %) (0.33-3.09%)	0.6%	-2.17-2.60%		2.04	0.23-18.08			
	8q16	163	0 (0 %) (0.00-2.24%)	-0.6%	-3.32-1.72%		NA	NA			
Week 60:	2q8	167									
	8q12	328	1 (0.6%) (0.02-3.29%) 4 (1.2%) (0.33-3.09%)	0.6%	-2.17-2.60%		2.04	0.23- 18.08			
	8q16	163	1 (0.6%) (0.02-3.37%)	0.0%	-2.76-2.85%		1.02	0.06-16.24			
Week 96:	2q8	167									
	8q12	328	2 (1.2 %) (0.15-4.26%)		-2.85-2.54%		1.27	0.25- 6.49			

Results of PHOTON - NCT04429503											
				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		
	8q16	163	5 (1.5 %) (0.50-3.52%)	0.3%	-3.72-2.31%		0.51	0.05-5.59			
			1 (0.6 %) (0.02-3.37%)	-0.6%							
Any ocular TESAE in study eye										Proportion of participants with ocular treatment-emergent serious adverse events summarized descriptively by treatment group in the safety analysis set population.	
Week 48	2q8	167	1 (0.6 %) (0.02-3.29%)								
	8q12	328	2 (0.6 %) (0.07-2.19%)	0%	-2.74-1.69%		1.02	0.09-11.15			
	8q16	163	1 (0.6 %) (0.02-3.37%)	0%	-2.76-2.85%		1.02	0.06-16.24			
Week 60											

Results of PHOTON - NCT04429503											
				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		
	2q8	167	1 (0.6 %) (0.02-3.29%)								
	8q12	328	2 (0.6 %) (0.07-2.19%)	0.0%	-2.74-1.69%			0.09-11.15			
	8q16	163	1 (0.6 %) (0.02-3.37%)	0.0%	-2.76-2.85%		1.02	0.06-16.24			
							1.02				
Week 96											
	2q8	167	2 (1.2 %) (0.15-4.26%)								
	8q12	328	3 (0.9 %) (0.19-2.65%)	-0.3%	-3.41-1.67%			0.13-4.53			
	8q16	163	3 (1.8 %) (0.38-5.28%)	0.6%	-2.64-4.22%		0.76	0.26-9.08			
							1.54				

Results of PHOTON - NCT04429503											
				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		
Non-ocular TESAEs										Proportion of participants with non- ocular treatment-emergent serious adverse events summarized descriptively by treatment group in the safety analysis set population.	
Week 48	2q8	167	26 (15.6%) (10.43-21.97%)								
	8q12	328	52 (15.9%) (12.07-20.26%)	0.3%	-6.93-6.75%		1.02	0.66-1.57			
	8q16	163	22 (13.5%) (8.66-19.72%)	-2.1%	-9.81-5.67%		0.87	0.51-1.47			
Week 60:	2q8	167	32 (19.2%) (13.49-25.96%)								
	8q12	328	61 (18.6%) (14.53-23.24%)	-0.6%	-8.25-6.44%		0.97	0.66-1.43			
	8q16	163		-2.6%	-10.94-5.76%		0.86	0.54-1.38			

Results of PHOTON - NCT04429503											
				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		
			27 (16.6%) (11.21-23.18%)								
Week 96:	2q8	167									
	8q12	328	42 (25.1 %) (18.77-32.44%)	-2.3%	-10.56-5.45%		0.91	0.65-1.26			
	8q16	163	75 (22.9 %) (18.43-27.80%)	-1.2%	-10.52-8.11%		0.95	0.65-1.39			
			39 (23.9 %) (17.60-31.22%)								

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 3 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 resulting HR to an assumed 1-	

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		
								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 4 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 5 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 6 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 7 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 8 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 9 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						

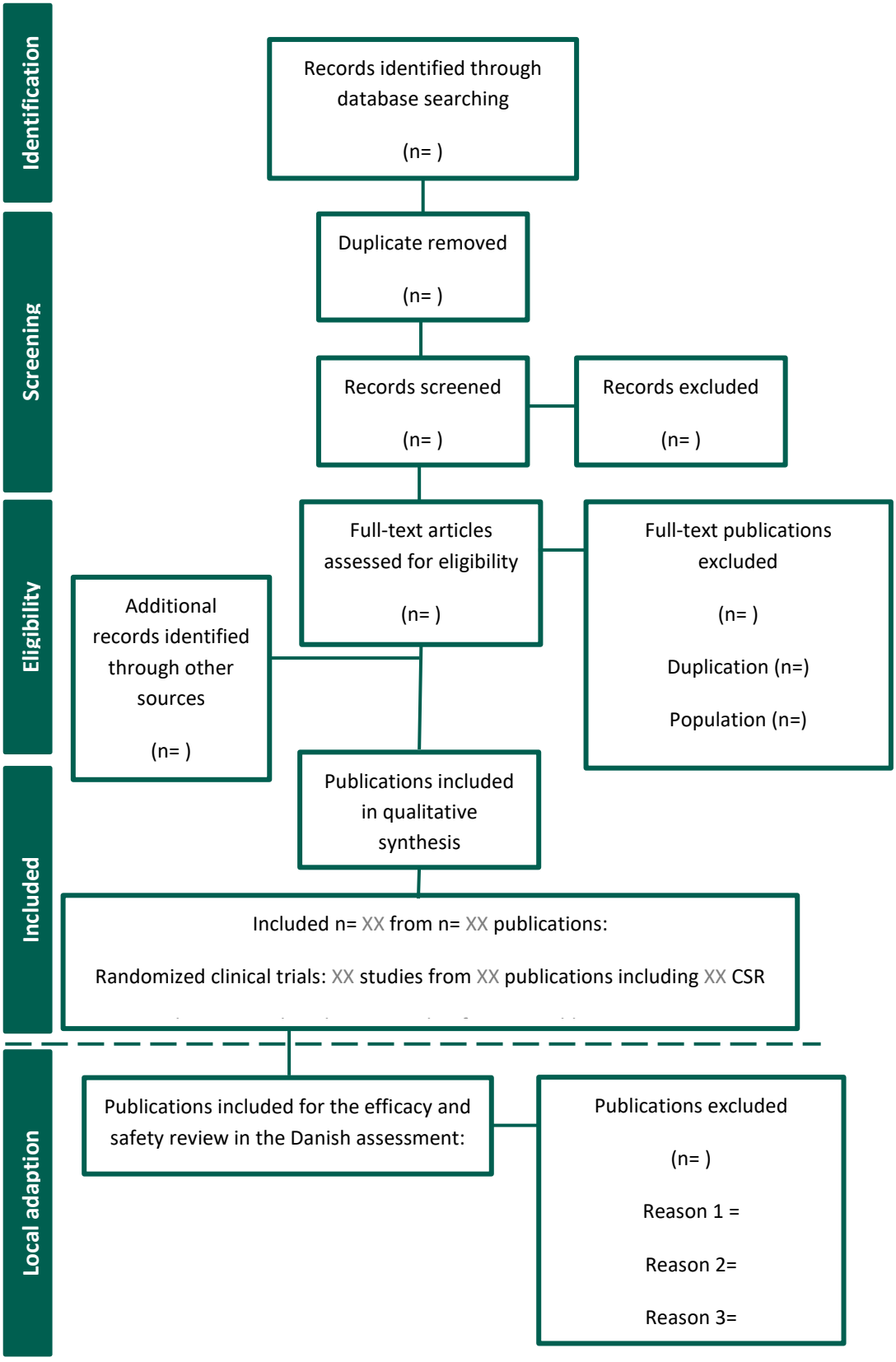
D.1.4 Quality assessment

[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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