11 December 2025
EMADOC-1700519818-2706650
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eylea

International non-proprietary name: Aflibercept

Procedure No. EMA/VR/0000264981

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ADA anti-drug antibody

ADR adverse drug reaction

AE(SI) adverse event (of special interest)

AMD age-related macular degeneration

ANCOVA analysis of covariance

APAC Asia-Pacific

APTC Anti-platelet Trialists' Collaboration

ATE arterial thromboembolic event

AUC0-28 mean area under the concentration-time curve from time zero to Day 28

BCVA best corrected visual acuity

BLA Biologics License Application

BRVO branch retinal vein occlusion

CI confidence interval

Cmax maximum (peak) concentration

CRT central retinal thickness

CRVO central retinal vein occlusion

CSR clinical study report

CST central subfield retinal thickness

DME diabetic macular edema

DNA desoxyribonucleic acid

DR diabetic retinopathy

DRM dose regimen modification

ECG electrocardiogram

EMA European Medicines Agency

ETDRS Early Treatment Diabetic Retinopathy Study

EU European Union

FA fluorescein angioscopy

FAS full analysis set

FDA Food and Drug Administration

FP fundus photography HD high dose

HRVO hemi-retinal vein occlusion

ICE intercurrent event

ICF informed consent

IOP intraocular pressure

IRF intraretinal fluid

IV intravenous

IVT intravitreal

LOCF last observation carried forward

LS least square MAR missing at random

MedDRA Medical Dictionary for Regulatory Activities

MMRM mixed model for repeated measurements

nAMD neovascular age-related macular degeneration

NEI-VFQ-25 National Eye Institute Visual Functioning Questionnaire-25

NI non-inferiority

OC observed cases

OCT optical coherence tomography

PCSV potentially clinically significant values

PD pharmacodynamic(s)

PK pharmacokinetic(s)

PlGF placental growth factor

Q4 every 4 weeks

Q8 every 8 weeks RVO vein occlusion

SAE serious adverse event

SAF safety analysis set

SAP statistical analysis plan

sBLA Supplemental Biologics License Application

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bayer AG submitted to the European Medicines Agency on 07 April 2025 an application for a group of variations.

The following variations were requested in the group:

The following changes were proposed:

Variation(s) requested		**Type**
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

A grouped application comprised of two Type II Variations, as follows: C.I.6.a: Extension of indication to include the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch, central and hemiretinal retinal vein occlusion, RVO) for EYLEA, based on results from study 22153 (QUASAR); this is a randomized, double-masked, active-controlled Phase 3 study of the efficacy and safety of aflibercept 8 mg in macular edema secondary to retinal vein occlusion. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. RMP version 36.1 has also been submitted. C.I.4: Update of section 4.2 of the SmPC in order to change posology recommendations of the approved indications neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) based on the results from study 22153 (QUASAR) and post-hoc analysis of the pivotal studies 20968 (PULSAR), 21091 (PHOTON) and Phase II study 21086 (CANDELA).

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Not applicable.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision(s) P/186/2011 and P/0165/2014 on the granting of a (product-specific) waiver.

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0115/2019 on the agreement of a paediatric investigation plan (PIP).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

Procedure	Date	Coordinators
EMA/SA/0000086937	23 June 2022	Silvijus Abramavicius and Andrea Laslop

The Applicant received Scientific Advice from the CHMP on the development of Aflibercept for the treatment of retinal vein occlusion from the CHMP on 23/06/2022 (EMA/SA/0000086937). The Scientific Advice pertained to the following clinical aspects of the dossier:

- Feedback on the proposal for one combined phase 3 study in CRVO and BRVO, including statistical considerations for the phase 3 study analysis, testing strategy, non-inferiority margins, dose and regimen of Eylea 2 mg as the comparator, the posology of the aflibercept 8 mg test treatment, the 28-week duration of efficacy data in the Phase 3 study and potential to support posology statements in the SmPC, use of a safety data set supplemented by data from studies of the aflibercept 8mg IVT in AMD and DME indications, with the provision of patient narratives for the RVO for treatment-emergent serious adverse events (SAEs).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Nicolas Beix Co-Rapporteur: n/a

Timetable	Actual dates
Submission date	07 April 2025
Start of procedure	26 April 2025
CHMP Rapporteur's preliminary assessment report circulated on:	23 June 2025
PRAC Rapporteur's assessment report circulated on:	23 June 2025
Updated PRAC Rapporteur's assessment report circulated on:	03 July 2025
PRAC comments	01 July 2025
PRAC outcome	10 July 2025
CHMP comments	10 July 2025
Updated CHMP Rapporteur's assessment report circulated on:	18 July 2025
Request for supplementary information (RSI) adopted by the CHMP on:	24 July 2025
MAH's responses submitted to the CHMP on:	12 August 2025
CHMP Rapporteur's preliminary assessment report circulated on:	17 September 2025
PRAC Rapporteur's preliminary assessment report circulated on:	17 September 2025
PRAC comments	24 September 2025
Updated PRAC Rapporteur's assessment report circulated on:	25 September 2025
PRAC outcome	02 October 2025

Timetable	Actual dates
CHMP comments	01 October 2025
Updated CHMP Rapporteur's assessment report circulated on:	09 October 2025
Second request for supplementary information (RSI) adopted by the CHMP on:	16 October 2025
MAH's responses submitted to the CHMP on:	10 November 2025
PRAC Rapporteur's preliminary assessment report circulated on:	17 November 2025
Updated PRAC Rapporteur's assessment report circulated on:	20 November 2025
CHMP Rapporteur's preliminary assessment report circulated on:	26 November 2025
PRAC outcome	27 November 2025
CHMP comments	01 December 2025
Updated CHMP Rapporteur's assessment report circulated on:	04 December 2025
CHMP opinion	11 December 2025

2. Scientific discussion

2.1. Introduction

This application contains two type II variations.

A type II variation category C.I.6.a to extend the therapeutic indication to include treatment of macular oedema secondary to retinal vein occlusion (RVO) based on the results from the pivotal Phase III study 22153 (QUASAR).

Another Type II variation category C.I.4 aims to change the minimum treatment interval in the posology section 4.2 of the approved indications nAMD and DME based on the results from QUASAR and post-hoc analysis of the pivotal studies PULSAR (nAMD), PHOTON (DME) and Phase II study CANDELA (nAMD).

Both label changes are submitted as a grouped variation because the combined analysis of the QUASAR, PHOTON, PULSAR and CANDELA studies, along with pharmacokinetic (PK) modelling, supports the need for a Q4 (every 4 weeks) dosing regimen during the maintenance phase, i.e. after the 3 initial monthly doses, for a small subset of patients. Three modelling and simulation reports are provided and analysed below: a population PK analysis B004119, an exposure-response analysis B004120, and a population PK/PD analysis B004121.

2.1.1. Problem statement

Disease or condition

Retinal Vein Occlusion (RVO) is among the most common causes of vision loss resulting from diseases that affect the retinal blood vessels. There are two primary types of RVO:

- Central Retinal Vein Occlusion (CRVO), which involves a blockage of the central vein responsible for draining blood from the retina, and
- Branch Retinal Vein Occlusion (BRVO), where one or more branches of the central retinal vein are obstructed.

- A less common subtype, Hemi-Retinal Vein Occlusion (HRVO), occurs when branches in either the superior or inferior hemisphere of the retina are blocked, sharing features of both CRVO and BRVO.

All RVO subtypes impair venous outflow from the eye, potentially leading to increased venous pressure, decreased arterial perfusion, and retinal ischemia. One of the consequences of retinal non-perfusion is elevated production of Vascular Endothelial Growth Factor (VEGF). In fact, VEGF levels in the aqueous humor of eyes with RVO can exceed normal levels by more than 100-fold.

This overexpression of VEGF promotes vascular permeability, macular oedema, retinal haemorrhages, and neovascularization. As a result, patients with macular oedema secondary to RVO experience loss of visual acuity, and without treatment, the visual prognosis is generally poor.

The claimed therapeutic indication

The claimed new indication for Eylea 114.3 mg/ml solution for injection and solution for injection in pre-filled syringe is:

Eylea is indicated in adults for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch, central and hemiretinal RVO) (see section 5.1).

2.1.2. About the product

Aflibercept as described in its SmPC is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors and thereby can inhibit the binding and activation of these cognate VEGF receptors.

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes and is also known to promote leucocyte infiltration and vascular inflammation.

nAMD is characterised by leakage of blood and fluid from a pathological choroidal neovascularisation (CNV) that may cause retinal thickening or oedema and/or sub-/intra-retinal haemorrhage.

DME is a consequence of diabetic retinopathy and is characterised by increased vaso-permeability and damage to the retinal capillaries.

RVO leads to impaired venous outflow from the retina, which can result in increased venous pressure, decreased arterial perfusion, and subsequent retinal ischemia.

Each pathology results in loss of visual acuity that, if left untreated can lead to blindness. The current standard of care (SOC) include treatment by anti-VEGF marketed products in Europe (EYLEA® – aflibercept; LUCENTIS® – ranibizumab and biosimilars; BEOVU® – broculizumab; VABYSMO® – faricimab), laser photocoagulation and vitrectomy.

Currently, EYLEA (aflibercept) 40 mg/mL solution for injection in pre-filled syringe and in a vial are registered via Centralised Procedure (EMA/H/C/002392) and are indicated in adults for the treatment of:

- neovascular (wet) age-related macular degeneration (AMD),

- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO),
- visual impairment due to diabetic macular oedema (DME),
- visual impairment due to choroidal neovascularisation (myopic CNV).

Although anti-VEGF therapy is the standard-of-care for nAMD, DME and RVO, the patients, physicians, and caregivers' burden remain consequent with regard to the long-term treatment and the related consequences related to the number of intravitreous (IVT) injections.

Therefore, the Applicant has developed a novel formulation (aflibercept 8mg) for IVT injections, which have the potential to decrease the number of IVT injections and at the same time increase intervals of patient's visits in adults for the treatment of nAMD and DME.

Currently, EYLEA (aflibercept) 114.3 mg/mL solution for injection in pre-filled syringe and in a vial are registered via Centralised Procedure (EMA/H/C/002392) and are indicated in adults for the treatment of:

- neovascular (wet) age-related macular degeneration (AMD),
- visual impairment due to diabetic macular oedema (DME).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The purpose of this Type II variation application is to seek marketing approval for extension of indication of aflibercept 114.3 mg/mL strength, for the already approved indication in the EU with the strength 40 mg/mL: retinal vein occlusion (RVO).

The clinical development program of aflibercept 8 mg to support efficacy and safety for the treatment of patients with RVO in this application consisted of one pivotal study:

- Study QUASAR (22153): an ongoing (with data through Week 64), multicenter, randomized, double-masked, active-controlled Phase 3 study in participants with RVO. Note: At the time of the variation submission, the study was still ongoing and was completed before the end of the procedure.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, aflibercept is not expected to pose a risk to the environment.

2.2.2. Discussion on non-clinical aspects

From a non-clinical point of view, no concern was identified which would argue against an extension of indication application.

2.2.3. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of aflibercept.

Considering the above data, aflibercept is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

This application contains two type II variations.

A type II variation category C.I.6.a to extend the therapeutic indication to include treatment of macular oedema secondary to retinal vein occlusion (RVO) based on the results from the pivotal Phase III study 22153 (QUASAR).

Another Type II variation category C.I.4 aims to change the minimum treatment interval in the posology section 4.2 of the approved indications nAMD and DME based on the results from QUASAR and post-hoc analysis of the pivotal studies PULSAR (nAMD), PHOTON (DME) and Phase II study CANDELA (nAMD).

Both label changes are submitted as a grouped variation because the combined analysis of the QUASAR, PHOTON, PULSAR and CANDELA studies, along with pharmacokinetic (PK) modeling, supports the need for a Q4 (every 4 weeks) dosing regimen during the maintenance phase, i.e. after the 3 initial monthly doses, for a small subset of patients. Three modelling and simulation reports are provided and analysed below: a population PK analysis B004119, an exposure-response analysis B004120, and a population PK/PD analysis B004121.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overview of the clinical efficacy study for HD aflibercept in the treatment of macular edema secondary to RVO

Study / Report location/ Study status	Study population /Analysis Sets	Efficacy-related objective	Study design and duration	Treatment: Dose, route of administration, frequency (number of participants randomized)
22153 (QUASAR) Module 5.3.5.1 QUASAR W36 CSR Results for all participants enrolled. Data cutoff for Efficacy/Safety: Week 36 visit for each participant The study is ongoing	**Phase 3:** Adult ≥ 18 years of age with treatment-naïve macular edema secondary to RVO (BRVO, CRVO or HRVO)	Primary efficacy objective: • To determine if treatment with aflibercept 8 mg Q8W provides non-inferior BCVA change compared to aflibercept 2 mg every 4 weeks (Q4W) Key secondary efficacy objectives: • Number of active injections from baseline to Week 64 [a]	Phase 3, randomized, double-masked, active-controlled study Duration: up to 67 weeks (including screening phase (3 weeks) and EoS (Week 64).	Aflibercept IVT, multiple dose: • 2q4 (n = 302): aflibercept 2 mg administered Q4W • 8q8/3 (n = 294): aflibercept 8 mg administered Q8W after 3 initial Q4W injections. • 8q8/5 (n = 298): aflibercept 8 mg administered Q8W after 5 initial Q4W injections. Treatment intervals were adjusted (based on DRM criteria) after 32 (2q4 and 8q8/3) or 40 (8q8/5) weeks of treatment

BCVA = best corrected visual acuity, CNV = choroidal neovascularization, DME = diabetic macular edema, DRM = dose regimen modification, EoS = end of study, HD = high dose aflibercept, Q4W = every 4 weeks, Q8W = every 8 weeks, IVT = intravitreal, n= number of participants, BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, HRVO = hemiretinal vein occlusion, RVO = retinal vein occlusion.

(a) The evaluation of the key-secondary endpoint will be included in the Week 64 CSR.

2.3.2. Pharmacokinetics

Bioanalysis

There are no changes in the bioanalysis methods. Validation report is provided.

Concentrations of free and bound aflibercept in plasma were measured using validated ELISA methods. The assay for bound aflibercept is calibrated using the VEGF:aflibercept standards, and the results are reported for bound aflibercept as weight per volume (e.g., ng/mL or mg/L) of the VEGF:aflibercept complex. To directly compare the relative concentrations (mg/L) of free and bound aflibercept it is first necessary to account for the difference in molecular weight and normalize the relative concentrations between free and bound aflibercept. The concentration of bound aflibercept is adjusted by multiplying the bound aflibercept:VEGF complex concentration by 0.717 (this is to account for the presence of VEGF in the bound complex) and is reported as mg/L (i.e., mass/volume). Throughout the associated CSRs and Clinical Pharmacology reports, concentrations of aflibercept:VEGF complex are limited to the adjusted bound aflibercept concentrations. The associated concentrations of bound aflibercept:VEGF complex are available in the Bioanalytical Sciences subreport for each CSR. The LLOQ for the free assay is 0.0156 mg/L or 0.0313 mg/L, depending on the assay used, and for the adjusted bound assay is 0.02244 mg/L or 0.0315 mg/L, depending on the assay used.

Population PK Analysis (Report B004119)

Background

A population PK analysis of aflibercept was conducted to characterize the PK of aflibercept in the RVO population and to compare these results with the nAMD and DME populations. Bayesian estimates of ocular clearance from the population PK analysis were utilized in exposure-response analyses to understand factors associated with dosing interval duration. The previous population pharmacokinetic dataset was updated to include the data and information from the QUASAR study.

Objectives

The primary objectives of the current population PK analysis were to:

• Evaluate and potentially refine the previously developed population PK model for aflibercept,

• Characterize the PK of free and adjusted bound aflibercept in patients with RVO in comparison to patients with nAMD or DME,

• Compare the accumulation of free and adjusted bound aflibercept in plasma after 3 or 5 initial monthly IVT injections.

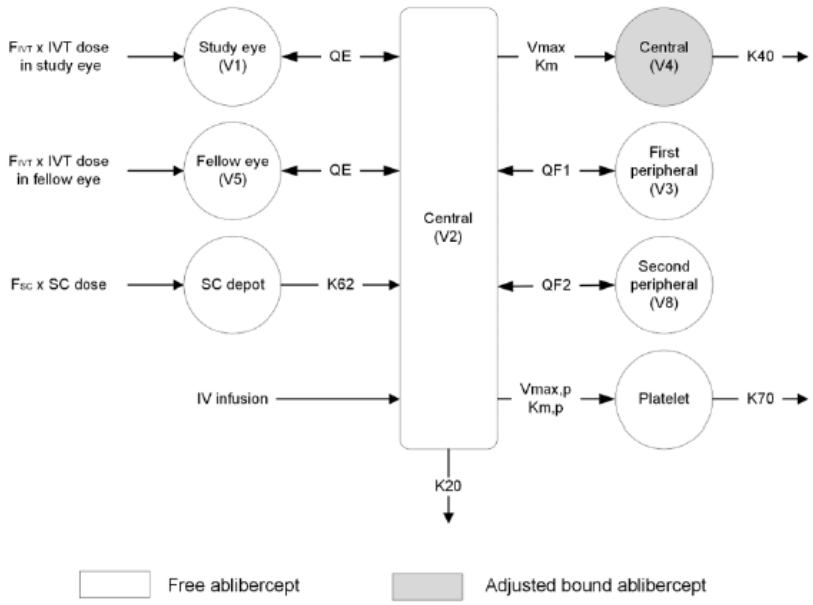
Methodology

Overall, the analysis dataset utilized in the current analysis included data from 17 clinical studies: 1 study in participants with RVO (QUASAR [86-5321-22153]), 13 studies in participants with nAMD or DME (VGFT-OD-0305, VGFT-OD-0306, VGFT-OD-0307, VGFT-OD-0502 [VGFTOD- 0502 part A and VGFT-OD-0502 part C], VGFT-OD-0512, VGFT-OD-0603, VGFT-OD- 0702.PK, VGFT-OD-0706.PK, 311523, CANDELA [VGFTe (HD)-AMD-1905], PHOTON [VGFTe (HD)-DME-1934], and PULSAR [86-5321-20968]), 2 studies in healthy male participants (PDY6655 and PDY6656), and 1 study in participants with solid tumors or lymphoma (TED6113).

This dataset comprised 883 participants with RVO, 1,662 participants with nAMD, 968 participants with DME, 76 healthy participants, and 38 oncology participants, i.e., in total 3,627 unique participants. A total of 19,238 free aflibercept concentrations and 19,296 adjusted bound aflibercept concentrations were included, with 61.7% and 16.1% of samples below the lower limit of quantitation (LLOQ) respectively. Across studies conducted in participants with nAMD, DME, or RVO, PK data were mostly collected using sparse sampling schedules, with limited samples obtained shortly after administration. While approximately 90% of participants with RVO had concentrations of free and adjusted bound aflibercept measured up to the Week 24 visit of the QUASAR study, only 274 out of 883 participants (approximately 31.0%) had measured concentrations in samples collected at the Week 36 visit. Overall, the QUASAR study contributed 883 participants with RVO with 7,208 samples records to the current analysis dataset.

Out of the 17 included studies, 4 studies (CANDELA, PHOTON, PULSAR, QUASAR) evaluated the safety, efficacy and PK of the HD drug product delivering 8 mg aflibercept versus the drug product delivering 2 mg aflibercept. It should also be noted that, contrary to the CANDELA, PHOTON, and PULSAR studies, the QUASAR study did not include any dense PK substudy in which a small fraction of the participants contributed data obtained via semi-dense schedules of plasma samples.

The previously developed population PK model (Population PK Report R-14326) was re-estimated using the current dataset based on the QUASAR Week 36 database lock. Because the prior model was developed sequentially and parameter estimates were fixed at various stages of analysis, only parameters that were estimated in the final stage of the prior analysis were reestimated. A schematic representation of the population PK model is provided in Figure below.



F_{IVT}=bioavailability after IVT dosing; F_{SC}=bioavailability after SC dosing; IV=intravenous; IVT=intravitreal; K_{20}=elimination rate constant of free aflibercept from the central compartment; K_{40}=elimination rate constant of adjusted bound aflibercept; K_{62}=absorption rate constant of free aflibercept from the SC depot compartment; K_{70}=elimination rate constant of free aflibercept from the platelet compartment; K_m=concentration of free aflibercept at half of maximum binding capacity with VEGF; $K_{m,p}$=concentration of free aflibercept at half of maximum binding capacity to platelets; Q_E=ocular clearance; Q_{F1}=first distribution clearance for free aflibercept; Q_{F2}=second distribution clearance for free aflibercept; SC=subcutaneous; V_1=volume of the study eye; V_2=volume of the central compartment for free aflibercept; V_3=volume of the first peripheral compartment for free aflibercept; V_4=volume of the central compartment for adjusted bound aflibercept (assumed to be the same as V_2); V_5=volume of the fellow eye; V_8=volume of the second peripheral compartment for free aflibercept; VEGF=vascular endothelial growth factor; V_{max}=maximum binding rate of free aflibercept to VEGF; $V_{max,p}$=maximum binding rate of aflibercept to platelets

Figure 1: model for aflibercept PK after IC, SC and IVT administration

Using the population PK model, post-hoc parameter estimates of the ocular clearance (QE) quantifying the bidirectional transfer of free aflibercept from the eye to the systemic circulation, metrics of systemic exposures (eg, Cmax, AUC, Ctrough), accumulation ratios, and time to reach the LLOQ in plasma, the impact of covariates on systemic exposure metrics, and the time for free aflibercept concentrations in the eye to reach various reference concentrations including multiples of the free aflibercept in vitro KD to VEGF-A were determined.

Results

Parameter estimates of the PK model are presented in table below. Overall, the estimates of the population PK model were very similar compared to the previous analysis and remained precisely estimated.

Table 2: Population PK Parameter Estimates for Aflibercept (Report B004119)

	Parameter	Estimate	95% CI	RSE (%)	Magnitude of variability (%)	Shrinkage (%)
Fixed effects for free aflibercept	F_{IVT}: Bioavailability after IVT injection (unitless)[a]	0.713	0.703, 0.724	0.761%	-	-
	Q_E: Ocular clearance for aflibercept 2 mg (mL/day)[a]	0.596	0.552, 0.638	3.93%	-	-
	QE ~ Proportional effect of HD aflibercept on QE (unitless)[a]	0.648	0.603, 0.697	3.72%	-	-
	QE ~ Power effect of age on QE (unitless)[a]	-1.35	-1.61, -1.16	7.99%	-	-
	V1: Volume of the eye (mL)[a]	4.00	Fixed	0%	-	-
	K20: Elimination rate constant (1/day)[b]	0.0807	0.0400, 0.126	29.5%	-	-
	K20 ~ Power effect of body weight on K20 (unitless)[b]	-0.192	-1.45, 0.714	234%	-	-
	V2: Volume of the central compartment (L)[b]	4.99	4.69, 5.22	2.79%	-	-
	V2 ~ Power effect of body weight on V2 (unitless)[b]	0.872	0.590, 1.22	19.3%	-	-
	V3: Volume of the first peripheral compartment (L)[b]	1.08	0.792, 1.56	17.0%	-	-
	V3 ~ Power effect of body weight on V3 (unitless)[b]	1.08	0.257, 2.71	51.3%	-	-
	V8: Volume of the second peripheral compartment (L)[b]	1.18	0.769, 2.07	39.8%	-	-
	V8 ~ Power effect of body weight on V8 (unitless)[b]	1.16	-0.962, 7.40	135%	-	-
	Q1: First distribution clearance (L/day)[b]	0.849	0.425, 1.26	29.2%	-	-
	Q2: Second distribution clearance (L/day)[b]	0.0763	0.0442, 0.110	23.7%	-	-
	VMAXP: Maximum binding rate to platelets (mg/day/L)[b]	0.0310	0.0148, 0.0649	35.3%	-	-
	KMP: Amount of free aflibercept at half Vmaxp (mg)[b]	42.7	2.16, 214	159%	-	-
	K70: Elimination rate constant from platelet (1/day)[b]	0.0265	0.00762, 0.105	99.0%	-	-
	FSC: Bioavailability after SC injection (unitless)[b]	0.536	0.487, 0.601	5.26%	-	-
	K62: Rate of absorption after SC injection (1/day)[b]	0.368	0.296, 0.430	10.5%	-	-
Fixed effects for adjusted bound aflibercept	V4: Volume of the central compartment (L)[b,c]	4.99	4.69, 5.22	2.79%	-	-
	V4 ~ Power effect of body weight on V2 (unitless)[b,c]	0.872	0.590, 1.22	19.3%	-	-
	VMAX: Maximum binding rate to VEGF in participants with nAMD, DME, or tumors (mg/day/L)[a]	0.218	0.212, 0.227	1.73%	-	-
	VMAX ~ Proportional effect in VMAX for healthy participants (unitless)[a]	0.631	0.602, 0.660	2.38%	-	-
	VMAX ~ Proportional effect in VMAX for participants with RVO (unitless)[a]	0.682	0.656, 0.704	1.97%	-	-
	KM: Concentration of free aflibercept at half Vmax (mg/L)[b]	0.411	0.272, 0.510	16.8%	-	-
	K40: Elimination rate constant (1/day)[d]	0.0350	0.0339, 0.0364	1.87%	-	-
	K40 ~ Power effect of body weight on K40 (unitless)[d]	-0.153	-0.251, -0.0768	27.8%	-	-

	K40 ~ Power effect of serum albumin on K40 (unitless)[d]	-0.767	-0.989, -0.599	14.0%	-	-
Inter-individual variability	ω2 in QE[a]	0.469	0.331, 0.644	16.9%	77.4%	32.3%
	ω2 in K20[b]	0.207	0.0917, 0.622	54.1%	48.0%	25.2%
	cov(ω2 in V2 and V4, ω2 in K20)[b]	-0.0727	-0.144, -0.0239	38.9%	-	-
	ω2 in V2 and V4[b]	0.0618	0.0251, 0.106	34.7%	25.3%	15.8%
	ω2 in VMAX[a]	0.104	0.0804, 0.149	16.7%	33.1%	40.6%
	ω2 in FSC[b]	0.629	0.278, 0.910	26.4%	36.8%	16.7%
	ω2 in K62[b]	0.852	0.261, 1.46	43.0%	116%	1.00e-10%
	ω2 in K40[d]	0.0452	0.0372, 0.0555	9.42%	21.5%	43.3%
Residual variability for free aflibercept	σadditive after IV + SC dosing when LLOQ is 0.0313 mg/L[d]	0.0250	0.00495, 0.0342	52.9%	40.3, 89.5%	-
	σproportional after IV + SC dosing when LLOQ is 0.0313 mg/L[d]	0.403	0.364, 0.461	5.97%		-
	σadditive after IV + SC dosing when LLOQ is 0.0156 mg/L[d]	0.00786	0.00591, 0.00913	11.8%	35.7, 61.8%	-
	σproportional after IV + SC dosing when LLOQ is 0.0156 mg/L[d]	0.357	0.324, 0.384	4.18%		-
	σadditive after IVT dosing when LLOQ is 0.0156 mg/L[a]	0.00664	0.00590, 0.00724	5.55%	41.5, 59.4%	-
	σproportional after IVT dosing when LLOQ is 0.0156 mg/L[a]	0.415	0.386, 0.435	3.39%		-
Residual variability for adjusted bound aflibercept	σadditive after IV + SC dosing when LLOQ is 0.0315 mg/L[d]	0.0206	0.0162, 0.0241	10.9%	16.7, 67.5%	-
	σproportional after IV + SC dosing when LLOQ is 0.0315 mg/L[d]	0.167	0.152, 0.186	5.07%		-
	σadditive after IVT dosing when LLOQ is 0.0315 mg/L[a]	0.0215	0.0172, 0.0256	10.4%	16.4, 70.2%	-
	σproportional after IVT dosing when LLOQ is 0.0315 mg/L[a]	0.162	0.121, 0.194	12.5%		-
	σadditive after IVT dosing when LLOQ is 0.0224 mg/L[a]	0.0263	0.0131, 0.0355	27.3%	20.6, 119%	-
	σproportional after IVT dosing when LLOQ is 0.0224 mg/L[a]	0.206	0.189, 0.231	5.31%		-

[a] estimates obtained from run077
[b] estimates obtained from run431
[c] set to the same values as V2-related estimates
[d] estimates obtained from run463
CI, Confidence intervals; HD, High dose (8 mg IVT cohorts); IV, Intravenous; IVT, Intravitreal; LLOQ, Lower limit of quantitation; RVO, Macular edema following retinal vein occlusion; RSE = Relative standard error; SC = Subcutaneous; VEGF = Vascular endothelial growth factor; σ, Standard deviation; ω2, Variance
Estimates of fixed-effect parameters are presented in the natural scale; interindividual variability terms are reported as variances around the log of the parameters or the logit of FSC. Magnitudes of residual variability are provided as ranges calculated at the maximum observed concentration of either free aflibercept or adjusted bound aflibercept and their respective LLOQ values based on route of administration. RSE are presented in the logit scale for FIVT and FSC and in the natural scale for all other parameters.
The following pairs of parameters were high correlated: VMAX: Maximum binding rate to VEGF and IIV in VMAX (r2 = 0.925)

The magnitude of shrinkage in Bayesian estimates of QE and Vmax in the final PK model reached 32.3% and 40.6%, similar to the values observed in the prior PK model. The magnitude of shrinkage in QE was just above the level of no concern and significantly below the threshold categorized as medium shrinkage level (45-65%). Therefore, the error associated with the post hoc estimates of QE is considered low. The only subsets of data in which the shrinkage in QE could be considered marginally medium in magnitude were the group of participants who received ≤ 4 mg IVT in the PHOTON study.

The population PK analysis concluded that the typical values of QE were not statistically different in participants with RVO, nAMD, or DME. In contrast, the inclusion of proportional shifts in Vmax for

participants with RVO and healthy participants led to a statistically significant improvement of the objective functions, and visible improvements of the predictive performance of the model assessed by prediction-corrected visual predictive check (pcVPC), especially in the data strata associated with adjusted bound aflibercept concentrations in participants with nAMD or DME.

In the final PK model, the typical estimates of QE and associated ocular elimination rate were estimated to be 35.2% slower after the injection of HD aflibercept than after 2 mg aflibercept (Table below). All estimates of fixed effects related to QE differed by ≤ 12.3% in the final population PK model compared to those obtained in the prior population PK model. The re-estimation of Vmax on the full analysis population and the addition of proportional shifts for participants with RVO and healthy participants resulted in a 30.5% increase in the typical estimate of Vmax which, in the final PK model, is representative of participants with nAMD, DME, or tumors. Vmax was estimated to be typically 36.9% and 31.8% lower in healthy participants and participants with RVO, respectively, than in participants with nAMD, DME, or tumors.

Table 3: Typical Estimate and 95% Confidence Interval of the Ocular Distribution

Drug product	Ocular clearance (mL/day)	Ocular elimination rate (1/day)	Ocular elimination half-life (day)
2 mg	0.596 (0.570, 0.624)	0.149 (0.142, 0.156)	4.65 (4.87, 4.44)
High Dose	0.387 (0.362, 0.413)	0.0966 (0.0905, 0.103)	7.17 (7.66, 6.72)

VPCs are presented below.

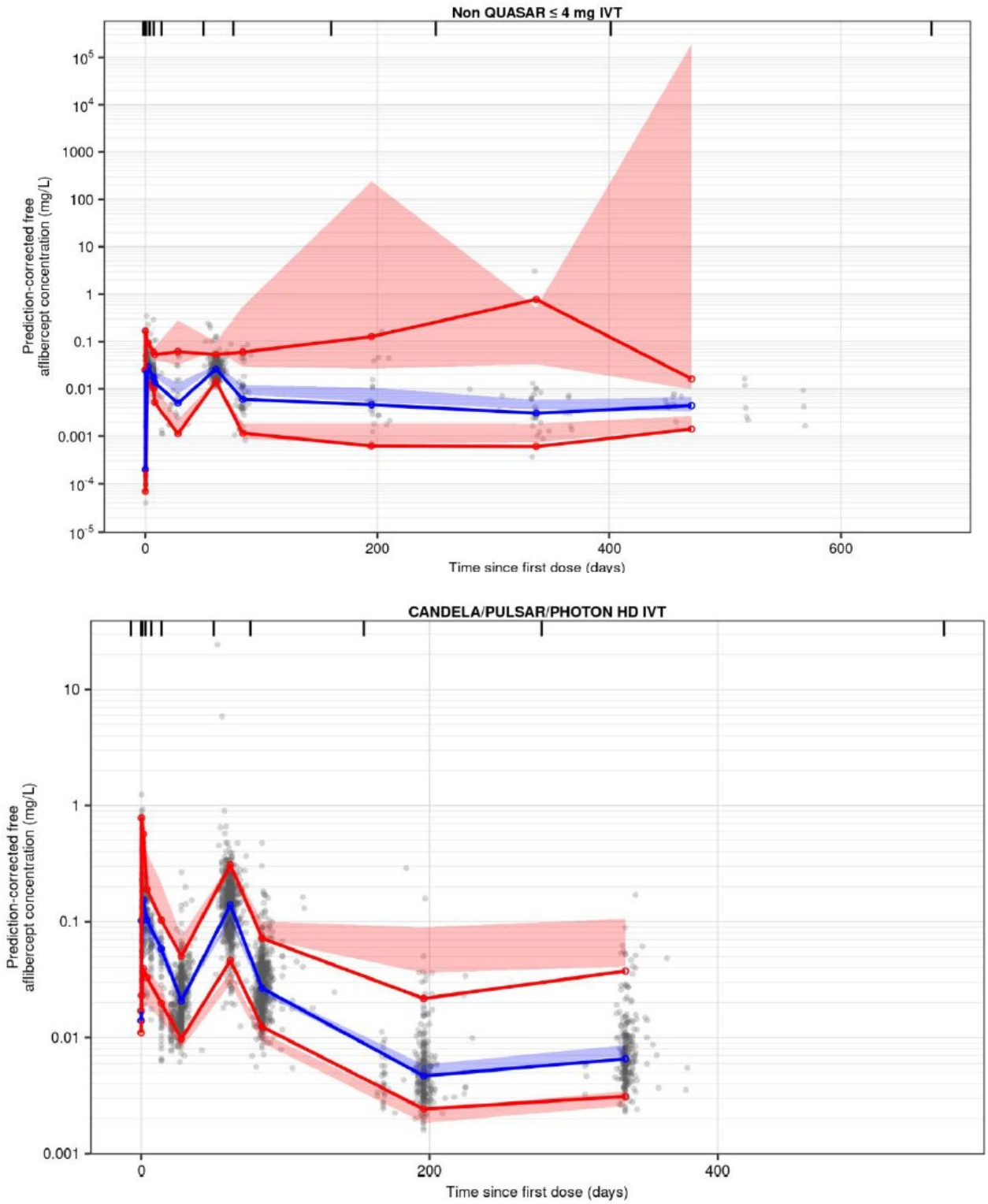
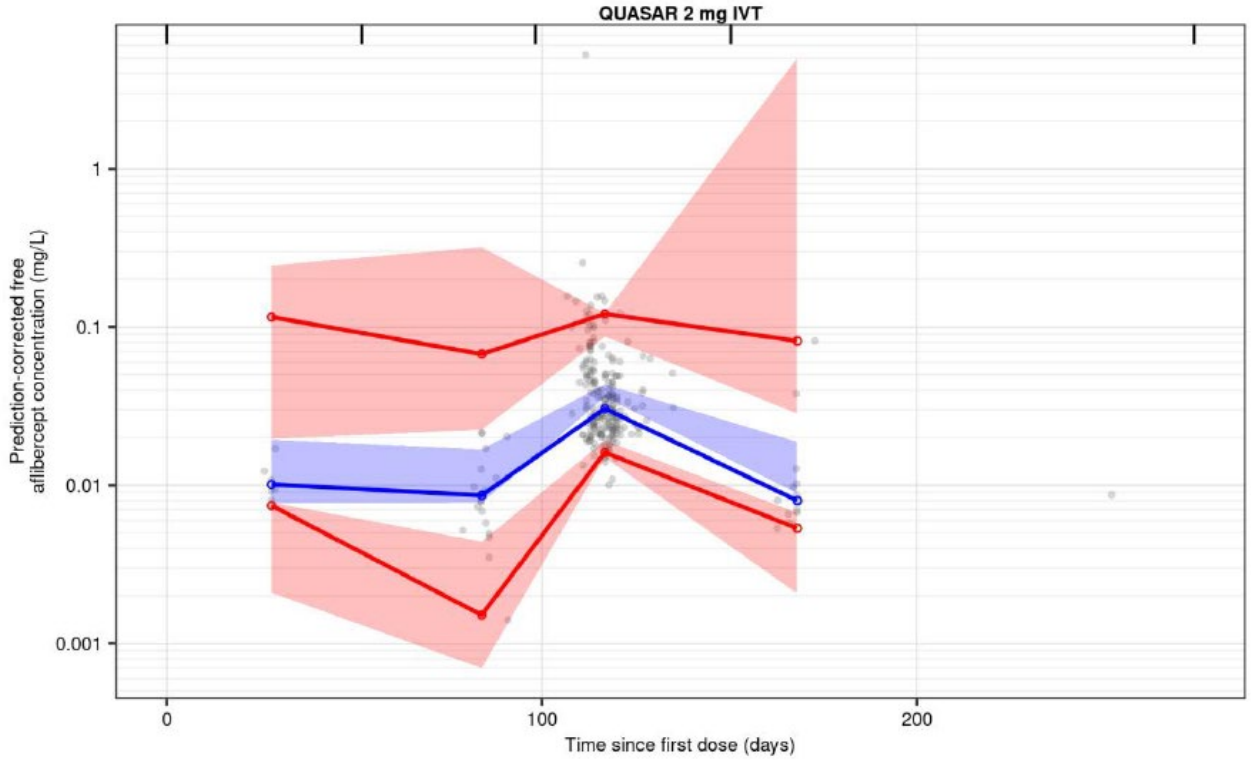


Figure 2: Prediction-corrected VPC plots for final PK model for free aflibercept after IVT administration



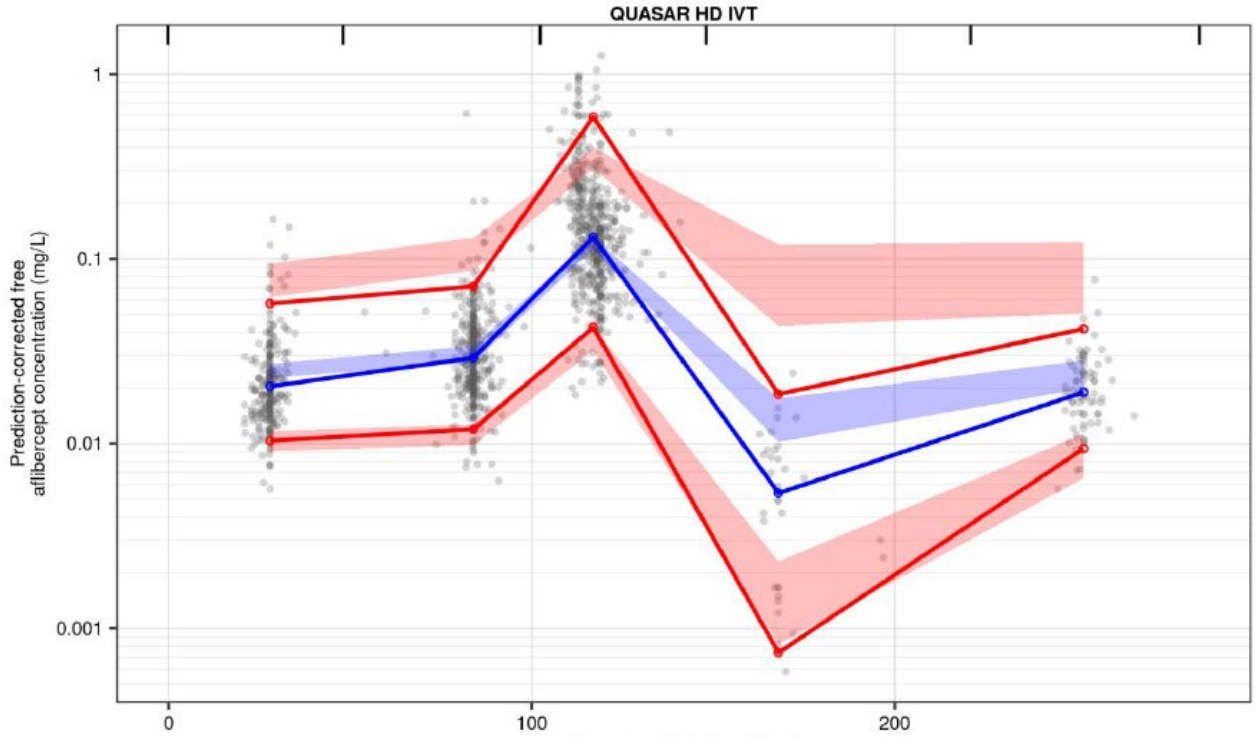


Figure 2: Prediction-corrected VPC plots for final PK model for free aflibercept after IVT administration (cont.)

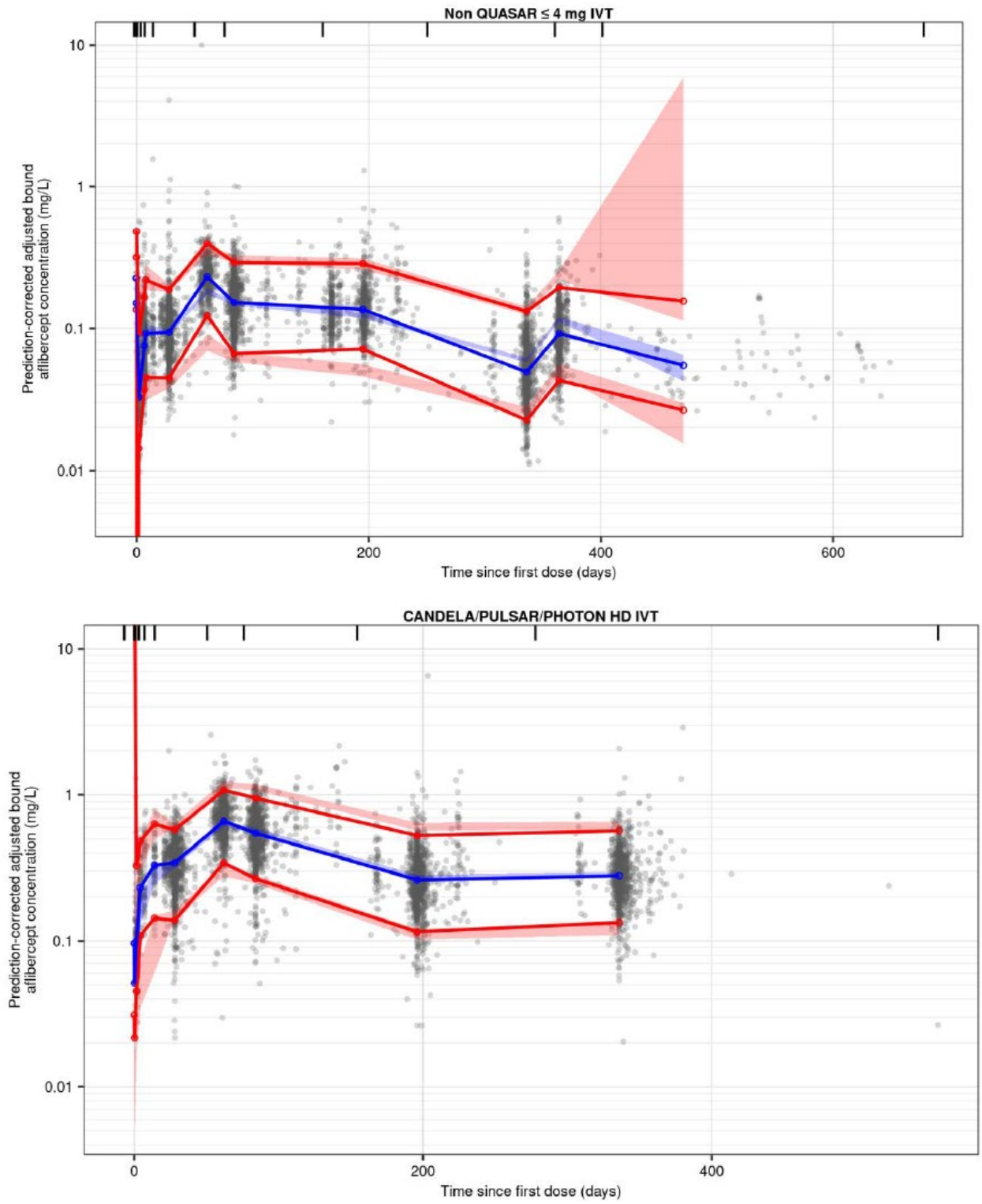


Figure 3:Prediction-corrected VPC plots for final PK model for adjusted bound aflibercept after IVT administration

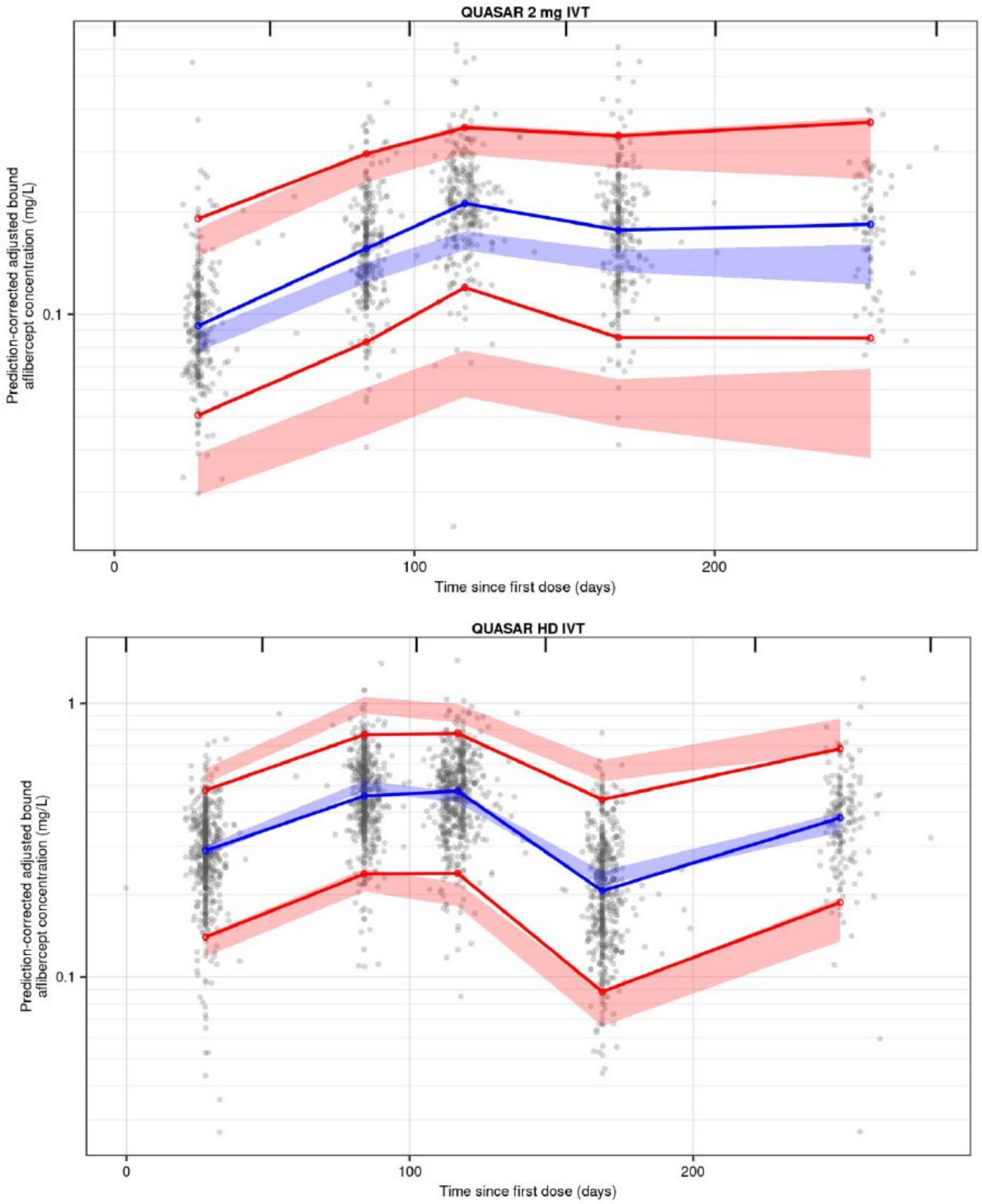


Figure 3: Prediction-corrected VPC plots for final PK model for adjusted bound aflibercept after IVT administration (cont.)

Table 4: Summary of Bayesian model predicted exposure metrics

Disease Population	n	Body Weight (kg)	$AUC_{week56-64}$ (mg x day/L)	$C_{max,week56-64}$ (mg/L)	$C_{max,week8-12}$ (mg/L)
Free aflibercept					
nAMD / DME	1687	80.9 (24.0%)	1.79 (54.2%)	0.122 (71.8%)	0.136 (65.4%)
MEfRVO	883	76.7 (24.1%)	2.40 (48.5%)	0.169 (60.9%)	0.185 (55.9%)
Adjusted bound aflibercept					
nAMD / DME	1687	80.9 (24.0%)	22.6 (44.9%)	0.539 (39.3%)	0.769 (37.3%)
MEfRVO	883	76.7 (24.1%)	20.1 (37.3%)	0.485 (32.4%)	0.689 (31.7%)

$AUC_{week56-64}$, Area under the concentration curve from weeks 56 to 64; CV, Coefficient of variation; $C_{max,week8-12}$, Maximum concentration from weeks 8 to 12; $C_{max,week56-64}$, Maximum concentration from weeks 56 to 64; DME, Diabetic macular edema; HD, High dose; MEfRVO, Macular edema following retinal vein occlusion; n, Number of participants; nAMD, Neovascular age-related macular degeneration

Note: Data are presented as arithmetic mean (CV%). Exposures were simulated using post-hoc pharmacokinetic estimates of participants from the CANDELA, PULSAR, PHOTON, and QUASAR studies assuming 3 monthly injections of aflibercept HD followed by one injection every 8 weeks for all participants.

Importantly, after accounting for difference in age distribution and the associated covariate effect on QE, the distribution of individual estimates of QE for the final PK model was similar across participants with RVO, nAMD, or DME. This indicated that the ocular clearance of aflibercept is predicted to be similar in patients of identical age, regardless of RVO, nAMD, or DME disease.

Conclusion by the applicant

An existing population PK model for free and adjusted bound aflibercept after SC, IV, and IVT administration was refined using data collected in participants with macular edema following RVO enrolled in the QUASAR studies. The distribution of estimated QE was similar across participants with macular edema following RVO, nAMD, and DME, once the differences that exist in age between the populations were taken into account. In the final PK model, the typical estimates of QE and associated ocular elimination rate were estimated to be 35.2% slower after the injection of HD aflibercept than after 2 mg aflibercept. Additionally, this analysis indicated that there was a 34 to 38% increase in systemic exposure to free aflibercept and a 9 to 10% decrease in systemic exposure to adjusted bound aflibercept, in participants with RVO compared to participants with nAMD or DME after Q8W administration of HD aflibercept administrations following 3 initial monthly IVT injections.

Additionally, this analysis indicated that, free aflibercept does not typically accumulate further in plasma between 3 and 5 initial monthly IVT injections, and the accumulation of adjusted bound aflibercept after 5 initial monthly IVT injections was approximately 10 to 14% greater than following 3 monthly IVT injections.

Absorption

Age was identified as an intrinsic covariate affecting ocular clearance of free aflibercept. After accounting for age, ocular clearance of free aflibercept was similar in the RVO, nAMD, and DME populations. These findings indicate that ocular clearance of free aflibercept is similar in patients of similar age, and that ocular disease itself does not affect the ocular clearance of free aflibercept.

Ocular clearance of free aflibercept was 35.2% slower for HD IVT aflibercept compared to 2 mg IVT aflibercept, which is attributed to an HD drug product effect, which was identified as the second statistically significant covariate in the population PK model. Based on the higher delivered dose and

slower ocular clearance of aflibercept 8 mg versus 2 mg, the population PK estimated median time that it takes for free aflibercept concentrations in the ocular compartment to reach the trough concentration at the end of a 4-week dosing interval for the 2q4 regimen occurs 4.1 weeks later after dosing of aflibercept 8 mg than after dosing of aflibercept 2 mg. Consistent with the model-estimated 4.1-week longer time to reach the 2q4 trough concentration in the eye, HD aflibercept administered at an interval 4 weeks longer (8q8/3, 8q8/5) than that for the 2q4 regimen demonstrated non-inferior efficacy in BCVA mean change from baseline at Week 36 in the QUASAR study.

Additional simulations predict that 12 weeks after an IVT dose of HD aflibercept or 2 mg aflibercept, free aflibercept concentrations in the eye remain above those at 9x the in vitro KD for binding to VEGF, i.e. the free aflibercept concentrations required to inhibit VEGF-A by 90% in an in vitro setting, in 77.7% of participants for HD aflibercept, compared to only 51.5% of participants for 2 mg aflibercept. Thus, ocular VEGF is expected to be inhibited for an extended duration in a considerably higher percentage of patients for HDq8 aflibercept compared to 2q4 aflibercept.

Distribution

Based on population PK analysis, the bioavailability of free aflibercept following IVT administration is estimated to be approximately 71%, and a median tmax of 2.85 days and a mean Cmax of 0.315 mg/L in plasma for a single 8 mg dose of HD aflibercept.

The total volume of distribution of free aflibercept after intravenous administration is estimated via population PK analysis to be approximately 7 L.

Elimination

The elimination of aflibercept is governed by nonlinear target-mediated binding to systemic endogenous VEGF, as well as through a non-saturable clearance process, which includes degradation via protein catabolism by proteolysis. Based on the population PK analysis, the median time for free aflibercept concentration in plasma to reach the lower limit of quantitation of the bioanalytical assay following an 8 mg IVT dose was 3.5 weeks.

Dose proportionality and time dependencies

Based on population PK analysis, free and adjusted bound aflibercept post-hoc estimated systemic exposure metrics indicated that, following single IVT doses of 2 mg or 8 mg aflibercept, mean area under the concentration-time curve from time zero to day 28 (AUC0-28)and Cmax of free aflibercept increase in a greater than dose-proportional manner (exposure ratio of 10.4 for AUC0-28 and 9.4 for Cmax) while mean AUC0-28 and Cmax of adjusted bound aflibercept increase in a slightly less than dose-proportional manner (exposure ratio 3.6 for AUC0-28 and 3.7 for Cmax).

These results are consistent with the known target-mediated related nonlinear PK of free and adjusted bound aflibercept.

Special populations

Age and HD drug product effect (formulation) were identified as statistically significant covariates in the population PK model affecting ocular clearance of free aflibercept.

Amongst the other covariates evaluated in the population PK analysis, body weight was the covariate with the greatest impact on systemic exposures to free and adjusted bound aflibercept, but resulted in only small effects as free and adjusted bound aflibercept Cmax and AUC increased $\leq$ 44% for

participants in the lowest body weight quintile (36.0 to 63.5 kg) compared to those in reference body weight group (72.6 to 81.6 kg). The small increases (≤ 34%) in systemic exposures to free and adjusted bound aflibercept in Asian and Japanese participants relative to their reference White or non-Japanese comparator groups are explained by differences in body weight, and indicate that a participant of Asian or Japanese origin with the same body weight as a White or non-Japanese participant will have similar systemic exposures to free and adjusted bound aflibercept. The effects of other evaluated covariates (age, albumin, and disease population) on systemic exposures to free and adjusted bound aflibercept also were small (≤ 34% increase relative to each respective reference comparator group). No dosage adjustments of HD aflibercept are warranted based on these assessed covariates.

For participants with mild to severe renal impairment, the small increases (≤ 37%) in systemic exposure to free and adjusted bound aflibercept relative to participants with normal renal function are accounted for by differences in body weight, indicating that renal impairment does not have a direct effect on aflibercept systemic exposures. Systemic exposures to free and adjusted bound aflibercept in participants with mild hepatic impairment were up to 16% lower compared to participants with normal hepatic function. No dosage adjustments of aflibercept are warranted for these populations.

Samples for immunogenicity assessments were not collected in QUASAR. In the pivotal studies PULSAR (nAMD) and PHOTON (DME), the incidence of treatment-emergent ADA through the end of the main study at Week 96 in the combined HD aflibercept treatment groups was 3.6% (37/1029 participants with nAMD [PULSAR] or DME [PHOTON]).

2.3.3. Pharmacodynamics

Mechanism of action

Aflibercept belongs to the pharmacological class of VEGF inhibitors. The role of VEGF in promoting pathological neovascularization and/or abnormal and excessive vascular permeability in several diseases affecting the eye is well established.

Exposure-Response Analyses for RVO (Report B004120)

Prior analyses indicated that high ocular clearance and high baseline CRT are predictors of the need for dose interval shortening from Q12 or Q16 to Q8 in patients with nAMD or DME.

In the QUASAR study, participants randomized to 8q8/3 or 8q8/5 HD aflibercept were eligible to have their dosing interval shortened beginning 8 weeks after the last initial monthly dose to a minimum interval of Q4. Descriptive analyses were performed to evaluate participant characteristics associated with shortening the dosing interval to Q4 in these participants with RVO.

The objective was to compare the characteristics of participants that were randomized to HD aflibercept and had their dosing interval shortened to Q4 against the characteristics of participants randomized to HD aflibercept and did not have their dosing interval shortened to Q4. The analysis dataset used for the pharmacometrics analyses included data collected during the conduct of the QUASAR study. The master PK/PD dataset was constructed by including PD-related data into the population PK analysis dataset used in the population PK analysis of the QUASAR study, as well as the ocular clearance (QE) estimates from the final population PK model.

Individual participant ocular clearance, baseline CRT, and baseline BCVA values were summarized and presented in graphical form. Distributions of these parameters were summarized by participants whose dosing interval was shortened to Q4 after previously extending to Q8 dosing versus those who were

able to maintain Q8 dosing and stratified by HD aflibercept regimen, 8q8/3 or 8q8/5. All analyses were descriptive, and no statistical analyses were performed.

Most of the patient characteristics evaluated showed no obvious difference for participants whose dosing interval was shortened to Q4 after extension to Q8 versus those whose dosing interval was not shortened to Q4. However, median ocular clearance and median baseline CRT was 32.3% higher and 6.5% higher, respectively, in participants whose dosing interval was shortened to Q4 after extension to Q8 dosing compared to those whose dosing interval was not shortened to Q4. A higher proportion of participants had their dosing interval shortened to Q4 after extension to Q8 dosing in the 8q8/3 group (10.9%) compared to the 8q8/5 group (6.04%), and this difference is likely attributable to participants in the 8q8/3 group having a longer period of time for DRM in the study(20 weeks) compared to the 8q8/5 group (12 weeks).

2.3.4. PK/PD modelling

Population PK/PD Analysis for nAMD and DME (Report B004121)

Background

To explore whether factors associated with dosing interval shortening to Q4 in RVO patients play a similar role in the other diseases HD aflibercept is already approved for, descriptive and model based analyses were performed to evaluate PHOTON and PULSAR participant characteristics associated with the need for shortening the dosing interval to Q4 after shortening to Q8 and to predict visual outcomes in these participants with DME or nAMD using clinical trial simulations.

While a majority of participants randomized to HDq12 or HDq16 regimens in PULSAR and PHOTON maintained their 12-week or 16-week dosing intervals through Week 48, 20.6% and 12.8% of the participants in PULSAR, and 9.0% and 3.8% of the participants in PHOTON, randomized to HDq12 or HDq16, respectively, had their dosing interval shortened to Q8. A post-hoc analysis indicated that a small proportion of the participants with nAMD (6.2%) or DME (1.5%) in PULSAR and PHOTON who had their dosing interval shortened from Q12 or Q16 to Q8 in year 1 met the protocol-specified criteria for a further shortening of their dosing interval to Q4, but were not shortened as the protocol-specified minimum dosing interval was Q8.

Objectives

The objectives of these analyses were to:

• Explore the characteristics of patients enrolled in the PHOTON and PULSAR studies who met DRM criteria after receiving HD aflibercept Q8, but were not dosed Q4 as per study protocol;

• Develop PK/PD models to characterize the relationship between aflibercept concentration in the eye with CRT and BCVA during the first year of the PULSAR and PHOTON studies for patients receiving HD aflibercept;

• Investigate through simulations the duration of effect after dosing HD aflibercept across the range of ocular clearance values seen in the PHOTON and PULSAR studies; and

• Infer through clinical trial simulations the expected BCVA response for HD aflibercept dose-interval shortening down to Q4 in virtual patients that fail to maintain response i.e., patients that still meet DRM criteria after having their dosing interval shortened to Q8.

Methodology

The analysis dataset used for the E-R analyses included clinical data collected from participants randomized to HD aflibercept during the first year of the PULSAR (PULSAR W48 CSR) and PHOTON (PHOTON W48 CSR). Bayesian estimates of ocular clearance of free aflibercept (QE) were derived from the population PK model based on the Week 96 database lock.

A small proportion of participants with nAMD or DME in PULSAR and PHOTON met the protocol-specified criteria for shortening their dosing interval from Q12 or Q16 to Q8 and continued to meet these criteria despite dosing at a Q8 interval, indicating a need for more frequent dosing (ie, Q4). For descriptive exposure-response analyses, individual participant QE and baseline CRT were summarized by the need for interval shortening to Q4 (yes/no) and by study. Participants in the HDq12 and HDq16 groups were pooled within the PULSAR and PHOTON studies. Joint longitudinal PK/PD models describing the relationship between free aflibercept concentration in the study eye and the endpoints CRT and BCVA were developed in each disease population independently (Figure 4). A sequential approach was applied to first characterize the relationship between free aflibercept concentration in the eye and CRT, and then, the relationship between CRT and BCVA. Finally, a parametric time-to-event model was developed to describe the rate at which patients were lost to follow-up.

Multiple criteria were applied to assess the appropriateness of the selected PK/PD models, including patterns in standard diagnostic plots, precision in final parameter estimates and pharmacological plausibility. The adequacy of the population model to describe the observed data was evaluated through simulation-based methods, eg, visual predictive checks (VPCs).

To explore potential visual outcomes for the participants who had their dosing regimen extended to either HDq12 or HDq16 (after 3 initial monthly injections), met DRM criteria for dosing interval shortening to Q8, and continued to meet DRM criteria despite Q8 dosing but did not receive Q4 dosing because the minimal interval allowed per protocol was Q8, simulation datasets were created using individual participant-level data (randomization group, QE). These data and the population PK/PD models were utilized to simulate potential BCVA outcomes over a 1- year period for 2 dosing scenarios: one scenario where the shortest dosing interval allowed was Q4 (Q4 simulation protocol) and another where the shortest dosing interval allowed was Q8 (Q8 simulation protocol).

Two simulation datasets, one for the Q4 simulation protocol and one for the Q8 simulation protocol, comprised of identical virtual participants were created for the PULSAR study, and similarly two simulation datasets were created for the PHOTON study. Simulations were carried out for 1 year, for each scenario a hundred times, and were performed such that dosing was dynamically adapted during the extension phase based on simulated CRT and BCVA response and according to the protocol-specified DRM criteria in each study. Simulations were performed separately for the PULSAR and PHOTON studies.

Once the longitudinal CRT and BCVA simulations (with their corresponding dose adaptations) were completed, it was determined that only 9.5% to 14% of virtual participants with nAMD and 1% to 4% of virtual participants with DME continued to meet DRM criteria after having their dosing interval shortened to Q8 from Q12 (after 3 initial monthly injections) and after dosing at a Q8 interval. These results align with the observed proportion of patients in PHOTON that met the protocol-specified criteria for shortening their dosing interval to Q8, and continued to meet those criteria after dosing at a Q8 interval (1.5%), but was slightly above the observed proportion in the PULSAR study (6.2%). BCVA outcomes at the end of the 1-year simulation period were compared for the subset of virtual participants who continued to meet DRM criteria after having their dosing interval shortened to Q8 in the Q4 simulation protocol (that is, their dosing interval was further shortened to Q4) versus the Q8 simulation protocol (that is, their dosing interval remained at Q8). Mean difference in BCVA for the Q4

versus Q8 simulation protocols was determined for each of the 100 simulations, and the resulting median (95% PI) for these 100 mean differences in BCVA were reported separately for the PULSAR and PHOTON studies.

In addition, individual simulations were performed to predict BCVA outcomes over a 1-year period for the actual participants from PULSAR (N=39) and PHOTON (N=7) that continued to meet protocol-specified DRM criteria after receiving at least one Q8 dose according to 2 scenarios:

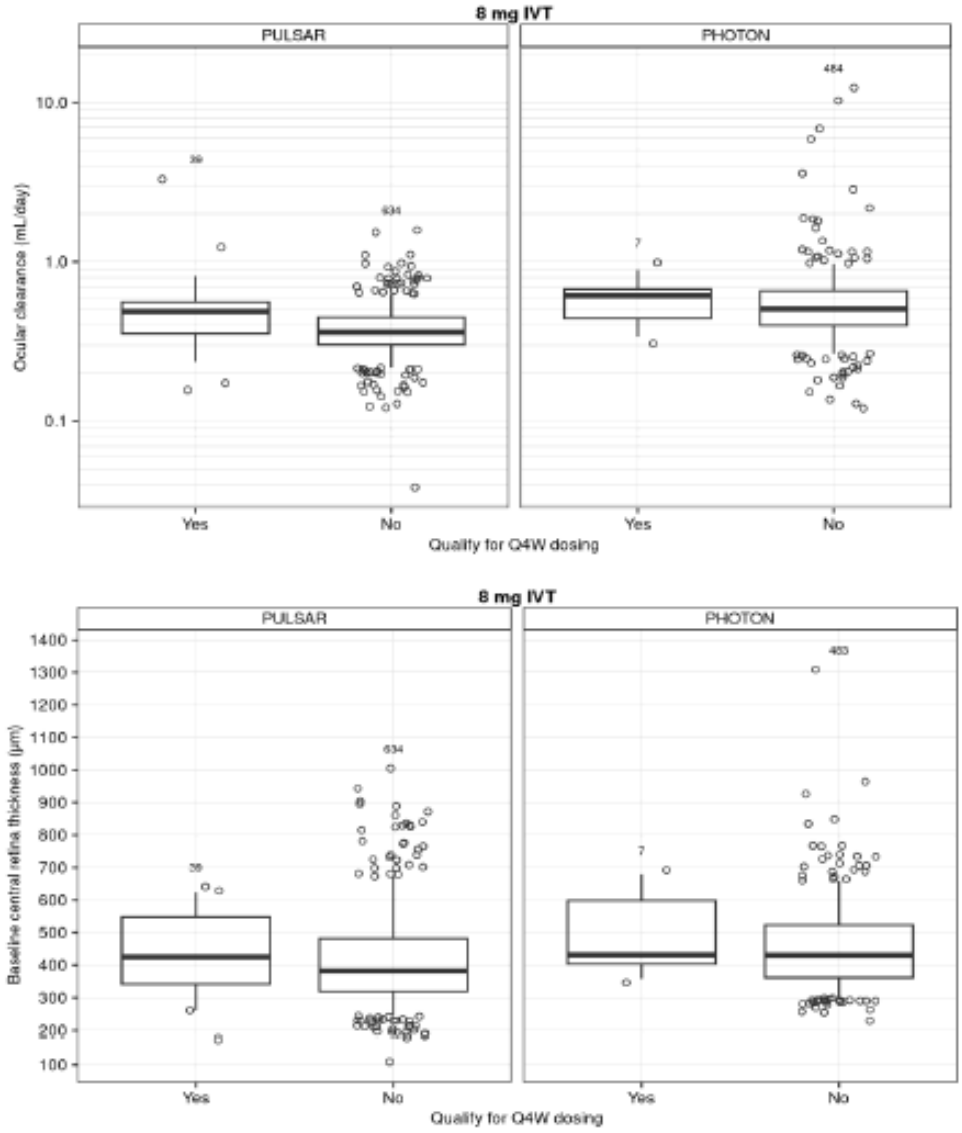
1) participants received Q4 dosing at the time they met DRM criteria for further interval shortening after receiving a Q8 dose; and

2) participants continued to receive Q8 dosing despite meeting DRM criteria for further interval shortening. As with the clinical trial simulations, their BCVA outcomes at the end of the 1-year simulation period were compared for the Q4 versus Q8 dosing scenarios.

Results

- Descriptive Exposure-Response Analyses

In the descriptive E-R analysis of participants with nAMD or DME (Figure below), median ocular clearance of free aflibercept was 34.2% higher and 20.8% higher in participants with nAMD (PULSAR) or DME (PHOTON), respectively, who continued to meet criteria for interval shortening after Q8 dosing compared to those who did not, with distributions overlapping between groups. A trend towards higher median baseline CRT was observed in participants who continued to meet DRM criteria to shorten their dosing interval despite dosing at a Q8 interval compared to those who did not (Figure below).



The boxes and whiskers delimit the interquartile ranges and 90% confidence intervals. The lines within boxes represent the medians of the data. The open circles represent the individual data outside the 90% confidence interval. The numbers represent the number of data points within each data sub-group.

Figure 4: Ocular Clearance (Top Panel) and Baseline CRT (Bottom Panel) in Participants by Continuing to Meet DRM Criteria for Shortening after Q8 Dosing (Yes/No), Stratified by Study (PULSAR, PHOTON)

Taking both ocular clearance and baseline CRT into account, the proportion of participants that continued to meet DRM criteria to shorten their interval after Q8 dosing in PULSAR was highest for participants having ocular clearance and baseline CRT above the median values of their respective groups (upper right quadrant, Figure 4). In contrast, the proportion of participants that met DRM criteria to shorten their interval after Q8 dosing was lowest for participants having ocular clearance and baseline CRT below the median values of their respective groups.

These results are consistent with prior results in participants with nAMD and DME and with those in the RVO population, and indicate that high ocular clearance and, to a lesser extent, high baseline CRT are characteristics associated with patients who might benefit (QUASAR) or might have benefitted (PULSAR and PHOTON) from Q4 dosing with HD aflibercept across all 3 populations.

- Model-based Exposure-Response Analyses

The results of the simulations indicate that, in the small proportion of virtual participants with nAMD or DME that continued to meet DRM criteria after having their dosing interval shortened to Q8, if they were to transition to Q4 dosing, they would have a mean gain in BCVA of 2.51 letters and 5.62 letters at the end of the 1-year simulation period, respectively, compared to the same virtual participants simulated to receive dosing no more frequently than Q8.

Simulations performed to predict BCVA outcomes over a 1-year period for the actual participants in PULSAR (N=39) and PHOTON (N=7) that continued to meet the DRM criteria after receiving at least one Q8 dose indicate - similar to the previous simulation - that these participants within AMD or DME who received Q4 dosing were estimated to have mean BCVA gains of 3.3 letters and 2.0 letters at the end of the 1-year simulation period, respectively, if they were to transition to Q4 dosing at the time they met DRM criteria after receiving a Q8 dose compared to the scenario where they received Q8 dosing despite meeting DRM criteria for further dosing interval shortening.

These model-based results indicate that participants with nAMD or DME who continue to meet clinical criteria to reduce the dosing interval after dosing Q8 are predicted to have better visual outcomes and clinical benefit if their dosing interval is reduced to Q4 compared to the scenario where the dosing interval remains no shorter than Q8. These predictions are consistent with the observations in participants in the QUASAR study who received HD aflibercept and continued to meet clinical DRM criteria for intensification of their dosing regimen after dosing Q8 (i.e., from Q8 to Q4) and that demonstrate that these participants received additional clinical benefit from the Q4 regimen.

2.3.5. Discussion on clinical pharmacology

Three modelling and simulation reports were provided to justify this variation: a population PK analysis B004119, an exposure-response analysis B004120, and a population PK/PD analysis B004121.

There are no changes in the bioanalysis methods.

The population PK model was modified to include the additional QUASAR data. Update of the model is well done; discussion of shrinkage is acceptable. VPCs show the model is appropriate. Overall, exposition between RVO and other authorised indications nAMD and DME can be considered similar, and the minimum treatment interval Q4 is also well defined for pharmacokinetics.

The population PK/PD analysis was also satisfactory and comforts the knowledge about the minimum dosing interval.

2.3.6. Conclusions on clinical pharmacology

Clinical pharmacology is acceptable and is in agreement with this variation.

2.4. Clinical efficacy

The MAH submitted a grouped type II variation for Eylea 114.3 mg/ml to update the product information:

- A type II variation under category C.I.6.a has been submitted to extend the therapeutic indication to include the treatment of macular edema secondary to retinal vein occlusion (RVO), supported on the results of the pivotal Phase III study 22153 (QUASAR). Accordingly, updates have been made to sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC, and the package leaflet has been revised to reflect these changes.

- A type II variation (C.I.4) has been submitted to revise the minimum treatment interval in SmPC section 4.2 for nAMD and DME, based on data from study 22153 (QUASAR) and post-hoc analyses of studies 20968 (PULSAR), 21091 (PHOTON), and 21086 (CANDELA).

The pivotal QUASAR study reports efficacy data through week 36 in 892 RVO patients.

The endpoints assessed the clinical benefit of high-dose aflibercept with extended dosing intervals, demonstrating equivalent or potentially superior visual and anatomical outcomes compared to aflibercept 2mg.

The primary efficacy endpoint was the change from baseline in BCVA, assessed by ETDRS letter score at week 36.

As the number of active injections is a relevant measure of treatment burden in both clinical studies and practice for RVO patients, the key secondary endpoint was defined as the number of active injections from baseline to week 64, with an additional secondary endpoint covering injections through week 36.

This submission also proposed an update to the approved dosing regimen for nAMD and DME to provide the option for monthly dosing (Q4) in a group of patients in need of more frequent maintenance dosing. The new indication, RVO, is intended to lessen the treatment burden for both patients and healthcare professionals by reducing the number of injections and clinic visits. The rationale provided is acceptable.

2.4.1. Main study(ies)

QUASAR Study – 22153

Methods

– Study design

QUASAR was a multi-center, randomized, double-masked, three-arm, active-controlled clinical trial designed to evaluate the efficacy and safety of high-dose (8 mg) intravitreal aflibercept compared to the approved 2 mg dose in patients with treatment-naïve macular edema resulting from retinal vein occlusion (RVO).

The study consists of a screening/baseline period, followed by a treatment period with duration of 60 weeks, and an end of study visit at Week 64.

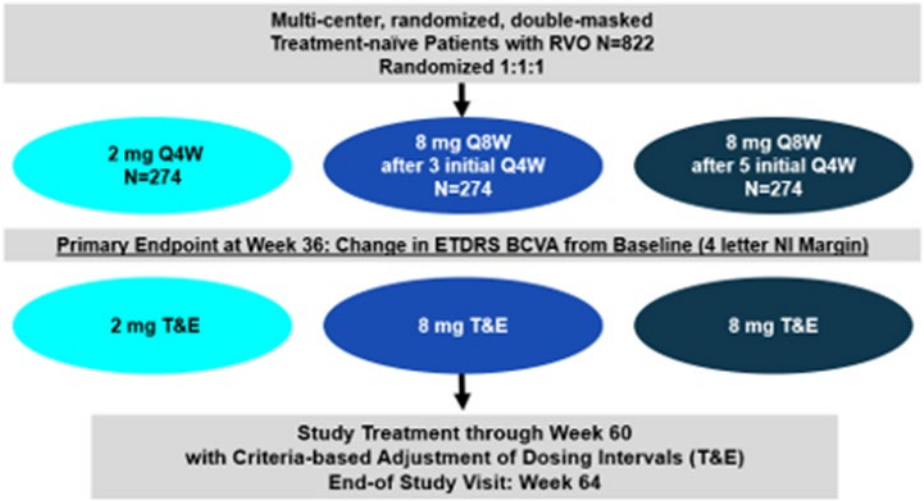
Participants who were eligible were randomly assigned in equal numbers to one of three treatment groups (1: 1: 1 ratio). Stratification applied to ensure balanced distribution of RVO subtypes (BRVO, HRVO, or CRVO) across all groups.

- 2q4: aflibercept 2 mg administered every 4 weeks until Week 32, followed by adjustment of treatment intervals according to treatment response.
- 8q8/3: aflibercept 8 mg administered every 8 weeks, with possible interval adjustments based on Dose Regimen Modifications criteria, following an initial loading phase of 3 injections given at 4-week intervals.
- 8q8/5: aflibercept 8 mg administered every 8 weeks, with possible interval adjustments based on Dose Regimen Modifications criteria, following an initial loading phase of 5 injections given at 4-week intervals.

The design of the study is depicted in Figure 5 and table 5 and 6.

Figure 5: QUASAR Study flow diagram

Sample sizes as planned in the protocol are given.



BCVA = best-corrected visual acuity, ETDRS = Early Treatment of Diabetic Retinopathy Study, NI = non-inferiority, Q4W = every 4 weeks, Q8W = every 8 weeks, RVO = retinal vein occlusion, T&E = treat and extend

Table 5: QUASAR: DOSING

Dosing intervals could be adjusted as specified in Table 2.

	Day 1	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36 prim. EP	Wk40	Wk44	Wk48	Wk52	Wk56	Wk60	Wk64 sec. EP
2q4	x	x	x	x	x	x	x	x	x	T&E	----------→						*no injections at Wk 64*
8q8/3	x	x	x	o	x	o	x	o	x	T&E	----------→						
8q8/5	x	x	x	x	x	o	x	o	x	o	x	T&E	----------→				

x = active injection o = sham injection grey shading = reference visit for dose regimen modifications
See Definitions of terms for explanation of treatment groups
prim. EP = primary endpoint, sec. EP = key secondary endpoint, T&E = treat and extend, Wk = week.

Table 6: QUASAR: Dose regimen modifications (DRMs)

	Possible start	Criteria
Shortening	2q4: Week 40 8q8/3: Week 16 8q8/5: Week 24	• BCVA loss > 5 letters from reference visit* and • CST increase > 50 µm from reference visit*
Extending	2q4: Week 32 8q8/3: Week 32 8q8/5: Week 40	• BCVA loss < 5 letters from reference visit* and • CST < 320 µm (incl. Bruch's membrane) < 300 µm (excl. Bruch's membrane)

* Reference visit 2q4: Week 20
8q8/3: Week 12
8q8/5: Week 20

See Definitions of terms for explanation of treatment groups
BCVA = best corrected visual acuity, CST = central subfield thickness, DRM = dose regimen modification

Study participants

Key inclusion criteria

1. Adult ≥ 18 years of age (or country's legal age of adulthood if the legal age is > 18 years) at the time of signing the informed consent.
2. Treatment-naïve macular edema involving the foveal center secondary to RVO (BRVO, HRVO or CRVO) diagnosed within 16 weeks (112 days) before the screening visit in the study eye.
3. BCVA letter score of 73 to 24 (20/40 to 20/320) at screening and baseline visits in the study eye.
4. Decrease in BCVA determined to be primarily the result of RVO in the study eye.
5. Mean CST ≥ 300 µm on OCT if excluding Bruch's membrane (e.g. Cirrus or Topcon) or ≥ 320 µm if including Bruch's membrane (e.g. Heidelberg Spectralis), confirmed by the reading center at the screening visit and by the site at baseline visit in the study eye.

Key exclusion criteria

1. Significant media opacities, including cataract, that interfere with BCVA, or imaging assessments (e.g. fundus photography [FP], optical coherence tomography [OCT]) in the study eye.
2. Aphakia, or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium-aluminum-garnet posterior capsulotomy performed more than 30 days before the screening visit), in the study eye.
3. Uncontrolled glaucoma (defined as IOP > 25 mmHg despite treatment with anti-glaucoma medication); or history or likely future need of glaucoma surgery in the study eye.
4. Intraocular inflammation/infection (including trace, or above, cells in the anterior chamber and/or vitreous) within 12 weeks (84 days) of the screening visit in the study or in the fellow eye.
5. Extraocular or periocular infection or inflammation (including infectious blepharitis, keratitis, scleritis, or conjunctivitis) in the study or in the fellow eye.
6. Uncontrolled blood pressure (defined as systolic > 160 mmHg or diastolic > 95 mmHg) at the screening visit or baseline visit.
7. Uncontrolled diabetes mellitus, defined by hemoglobin A1c (HbA1c) > 12% at the screening visit.
8. History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) before the screening visit or between screening and baseline visits.
9. Prior treatment of the study eye with any of the following drugs (any route of ophthalmic administration) or procedures:
   - Anti-angiogenic drugs at any time including investigational therapy (e.g. with anti angiopoietin/anti-VEGF bispecific monoclonal antibodies).
   - Previous use topical steroids within 4 weeks (28 days) from the screening visit, or intraocular or periocular steroids within 16 weeks (112 days) from the screening visit, or steroid implants at any time.

- Previous treatment with intraocular or periocular implant, gene therapy, or cell therapy at any time.
- Treatment with ocriplasmin at any time.
- Vitreoretinal surgery (including scleral buckling) at any time.
- Any intraocular surgery, including cataract surgery, within 12 weeks (84 days) before the screening visit.
- Previous treatment with retinal laser photocoagulation.

In accordance with the recommendations provided in the scientific advice (EMA/SA/0000086937), the Applicant stratified patients by RVO subtype to ensure balanced allocation across treatment groups.

Inclusion and exclusion criteria are considered relevant to select appropriately patients with CRVO, BRVO or HRVO. It is fully supported that the selection criteria should not exclude patients with ischemic RVO.

Treatments

In QUASAR study, patients were randomized in a 1:1:1 ratio to receive monotherapy in the treated eye with either 2 mg aflibercept (administered every 4 weeks until week 32, followed by adjustment of treatment intervals according to treatment response) or aflibercept 8 mg 8q8/3 or 8q8/5 (administered every 8 weeks after 3 initial Q4W or administered every 8 weeks after 5 initial Q4W).

The participants could benefit from a dose regimen modification according to pre-specified criteria listed in table 7.

Group Name	Aflibercept 8 mg	Aflibercept 2 mg	Sham	Diagnostic Agents
Intervention Name	Aflibercept 8 mg	Aflibercept 2 mg	Sham	Fluorescein sodium 100 mg/mL
Type	Drug	Drug	Not applicable	Dye
Dose Formulation	Solution in vial	Solution in vial	Not applicable	Solution in vial
Unit Dose Strength(s)	114.3 mg/mL	40 mg/mL	Not applicable	Not applicable
Dosage Level(s)	8 mg (70 µL)	2 mg (50 µL)	Not applicable	500 mg (5 mL)
Route of Administration	IVT injection	IVT injection	Not applicable	Intravenous injection
Use	Experimental	Active comparator	Sham procedure	Diagnostic
IMP/AxMP	IMP	IMP	IMP	AxMP
Packaging and Labeling	Study Intervention was provided in sterile 3 mL glass vials. Each vial was labeled as required per country requirement.	Study Intervention was provided in sterile 2 mL glass vials. Each vial was labeled as required per country requirement.	Empty kit	Sites used locally available commercial product in unchanged market packaging, used according to the approved label.

AxMP=auxiliary medicinal product (medicinal products used in the context of a clinical trial but not as investigational medicinal product), IMP=investigational medicinal product, IVT=intravitreal(ly)

Figure 6: study intervention(s) administered

Table 7: QUASAR: dose regimen modifications (DRMs)

	Possible start	Criteria
Shortening	2q4: Week 40 8q8/3: Week 16 8q8/5: Week 24	• BCVA loss > 5 letters from reference visit* and • CST increase > 50 µm from reference visit*
Extending	2q4: Week 32 8q8/3: Week 32 8q8/5: Week 40	• BCVA loss < 5 letters from reference visit* and • CST < 320 µm (incl. Bruch's membrane) < 300 µm (excl. Bruch's membrane)

* Reference visit 2q4: Week 20
8q8/3: Week 12
8q8/5: Week 20

See Definitions of terms for explanation of treatment groups
BCVA = best corrected visual acuity, CST = central subfield thickness, DRM = dose regimen modification

Permitted concomitant treatments:

Participants may not receive any standard or investigational agents for treatment of their macular edema secondary to RVO in the study eye other than assigned study treatment as specified in this protocol until they have completed the EoS/early discontinuation visit assessments. This includes medications administered locally (e.g., IVT, by juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating the study eye or the fellow eye.

Any medication considered necessary for the participant's welfare, and that is not expected to interfere with the evaluation of the study intervention, may be given at the discretion of the Investigator.

Any medication or vaccine (including any sedation, anesthesia, eye drops used for the study procedures, blood-derived products, prescription or over-the-counter medicines, probiotics, vitamins, and herbal supplements) that the participant receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency If a pre-treatment concomitant medication is administered in the study eye before injection (e.g., antibiotic, topical anesthetic), it must be administered for sham procedures as well. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Objectives

Primary objective

- To determine if treatment with aflibercept 8 mg Q8 provides non-inferior BCVA change compared to aflibercept 2 mg Q4

Secondary objectives

- To determine if treatment with aflibercept 8 mg Q8 requires less injections compared to aflibercept 2 mg Q4
- To determine the effect of aflibercept 8 mg Q8 compared to aflibercept 2 mg Q4 on other visual and anatomic measures of response
- To assess the efficacy of aflibercept 8 mg Q8 compared to aflibercept 2 mg aflibercept Q4 on vision-related QoL

Other secondary objectives

- To evaluate duration of effect of aflibercept 8 mg Q8 compared to aflibercept 2 mg aflibercept Q4
- To evaluate the PK of aflibercept 8 mg Q8 compared to aflibercept 2 mg aflibercept Q4

Exploratory objectives

- To determine the effect of aflibercept 8 mg Q8 compared to aflibercept 2 mg Q4 on further visual and anatomic measures of response
- To study molecular drivers of RVO or related diseases, clinical efficacy of aflibercept, and affected molecular pathways

Outcomes/endpoints

Primary efficacy endpoint

- Change from baseline in BCVA measured by the ETDRS letter score at Week 36

Key secondary efficacy endpoint

- Number of active injections from baseline to Week 64

Secondary endpoints

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

Additional secondary endpoints

- Participants dosed only Q8 through Week 36 in the 8 mg Q8 group
- Participant having last treatment interval ≥12 or of 16 weeks at Week 64
- Participant having next intended interval ≥12, ≥16 or of 20 weeks at Week 64
- Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Weeks 36 and 64

Exploratory endpoints

- Change from baseline in BCVA measured by the ETDRS letter score at each visit
- Participant with vision changes of at least 5, 10, or 15 letters in BCVA from baseline at each visit

- Participant with no IRF and no SRF in the center subfield at each visit
- Time to fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield)
- Participant having sustained fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield)
- Change in area of retinal ischemia at Weeks 36 and 64
- Change in the area of fluorescein leakage at Weeks 36 and 64
- Evaluation of clinical efficacy parameters by repertoire or frequency of genetic alterations (genomics substudy)
- Intervention-related changes in circulating biomarkers (FBR)

The primary objective of the study, which was to determine if treatment with aflibercept 8mg Q8 with two different loading dose administrations provides non-inferior BCVA change compared to aflibercept 2mg Q4, is supported for the assessment of non-inferiority and is in line with the initial Scientific advice EMA/SA/0000086937.

Secondary efficacy endpoints evaluate the number of active injections, change in BCVA, CST, presence/absence of intra/sub-retinal fluid from baseline at different time points over the study course. The secondary efficacy endpoints are therefore deemed acceptable.

- **Estimands for the primary objective**

Population	**Adult patients with treatment-naïve macular edema secondary to RVO.**
Treatment condition<s>	• Aflibercept 8 mg administered with 3 initial Q4 doses followed by extension of treatment interval to 8- weeks and further adjustment of intervals according to treatment response • Aflibercept 8 mg administered with 5 initial Q4 doses followed by extension of treatment interval to 8- weeks and further adjustment of intervals according to treatment response • Aflibercept 2 mg administered Q4 until Week 32, followed by adjustment of treatment intervals according to treatment response A delayed active injection resulting in an injection interval up to 4 weeks longer than planned is considered to be in line with the treatment regimen of interest.
Endpoint (variable)	Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 36
Population-level summary	Difference in mean change from baseline to Week 36 in BCVA between each aflibercept 8 mg group and the aflibercept 2 mg group
Intercurrent events and strategy to handle them	
Discontinuation of study treatment and of study for any reason before week 36	Hypothetical strategy addressed through a mixed model for repeated measures (MMRM)
Discontinuation of study treatment before week 36 but continuation of study	Hypothetical strategy addressed through a MMRM analysis but observed data beyond the last active injection + current treatment interval +5 days are excluded from analysis (considered as missing data)
Use of Prohibited concomitant medications before week 36	Hypothetical strategy addressed through a MMRM analysis, observed data beyond the administration of the prohibited treatment are excluded from analysis (considered as missing data)

Missed active injection resulting in an actual injection interval up to 4 weeks longer than planned	Treatment policy strategy, all available data are included in the MMRM analysis
Missed active injection resulting in an actual injection interval more than 4 weeks longer than planned	Hypothetical strategy addressed through a MMRM analysis, observed data beyond the last active injection + current treatment interval +5 days are excluded from analysis (considered as missing data)

Sample size

The sample size calculation was based on the primary efficacy estimand and its endpoint: the change from baseline in BCVA (Best Corrected Visual Acuity), measured by the ETDRS letter score at Week 36.

The sample size was determined using the following assumptions for both the 8 mg/5 group and the 2 mg group:

- BCVA letter score changes from baseline are normally distributed.
- The true difference in mean BCVA change between the 8 mg/5 and 2 mg groups is 0 letters.
- The standard deviation is 12.5 in both treatment groups, derived from an integrated analysis of GALILEO and COPERNICUS data.

Similar assumptions were applied to the 8 mg/3 group when compared to the 2 mg group.

A sample size of 246 evaluable participants per group provides approximately 90% power to reject the null hypotheses for both the first and second test problems in the hierarchical order. This is based on a 1-sided t-test at a significance level of 0.025.

Assuming about 10% of participants will drop out before Week 36 (the primary endpoint), approximately 274 participants need to be randomized per group. This leads to a total sample size of roughly 822 participants. To enable a supportive exploratory subgroup analysis for BRVO and CRVO/HRVO, the study aims to randomize a minimum of 40% of participants, or 329 participants, per RVO type ([CRVO or HRVO] vs. BRVO). With this sample size, there's approximately a 90% probability (given the assumptions mentioned earlier) that the 95% confidence interval for the difference between pooled aflibercept 8 mg and aflibercept 2 mg will exclude a margin of 5 letters in each subgroup.

Intercurrent Events

Premature discontinuation of study treatment (for any reason) is defined as an intercurrent event. The primary estimand will follow a hypothetical strategy, determining the treatment effect in a scenario where all participants continued their randomized treatment until Week 36.

Justification of Japanese sample size

Past aflibercept studies have shown no differences in response between Japanese and global study populations. This establishes that aflibercept (and other drugs in the anti-VEGF IVT Injection class) is ethnically insensitive, as concluded by the European Medicines Agency and the related U.S. Department of Health. To ensure appropriate representation within the overall study population and each subgroup, approximately 10% of the study participants are planned to be recruited in Japan.

Randomisation

A total of approximately 822 eligible participants with macular oedema secondary to retinal vein occlusion (RVO) were randomized in a 1:1:1 ratio to one of the following treatment groups:

- Aflibercept 8 mg every 8 weeks (Q8W) after 3 initial doses administered every 4 weeks (Q4W) [8 mg/3],
- Aflibercept 8 mg Q8W after 5 initial Q4W doses [8 mg/5], or
- Aflibercept 2 mg Q4W [2 mg].

At least 40% of eligible participants were expected to be enrolled in each RVO subtype stratum: central or hemi-retinal vein occlusion (CRVO/HRVO) and branch retinal vein occlusion (BRVO). Randomization was stratified by RVO type (CRVO or HRVO vs. BRVO), geographic region (Japan vs. Rest of Asia-Pacific [APAC] vs. Americas vs. Europe), and baseline best corrected visual acuity (BCVA) (<60 vs. ≥60 letters). For the purpose of stratification, HRVO participants were grouped under the CRVO stratum.

Blinding (masking)

An unmasked Investigator (or designated individual), distinct from the masked study personnel, was responsible for performing the active injection or sham procedure, post-injection indirect ophthalmoscopy, and intraocular pressure (IOP) assessments. To maintain blinding, participants must remain unaware of their treatment assignment; therefore, the study intervention and syringe must be concealed and rendered unidentifiable to the participant.

The unmasked Investigator's involvement in the study was limited to:
(i) the receipt, tracking, preparation, destruction, and administration of the study intervention, and
(ii) the reporting of any adverse events (AEs), serious adverse events (SAEs), or device deficiencies related to the filter needle, injection needle, or syringe during the post-injection phase.

An unmasked drug handler (e.g., a pharmacist) may be designated to manage the receipt, storage, and preparation of both active and sham intervention kits. Unmasked personnel may also conduct screening and baseline procedures, such as obtaining initial informed consent (however, any re-consent must be carried out by masked staff).

The randomization was performed through an interactive response system allocating treatments from a predefined randomization list. It included 3 stratification factors: the RVO type (2 strata), the geographical region (4 strata) and the visual acuity baseline (2 strata). Subgroup analyses should describe these strata. The handling of masking procedures appears reliable. The difference in loading doses prior the extension period of treatment is masked through sham injections when needed.

Statistical methods

Populations for analysis

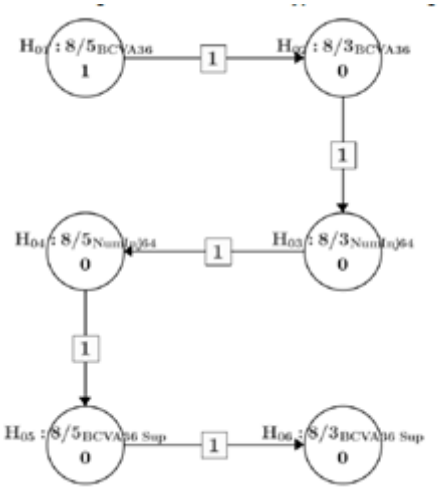
Efficacy analyses were conducted exclusively on the Full Analysis Set (FAS), which comprised all randomized participants who received at least one dose of the study intervention (active or sham). Participants were analyzed according to their initial randomization group (intention-to-treat principle).

FAS (Full Analysis Set) analysis most closely resembles real-world data usage and appears to be the most suitable for analysis. However, it is known that this population could, to some extent, artificially favour the non-inferiority demonstration. Therefore, a per-protocol population analysis was asked to be

performed as well to check the robustness of the FAS analysis, unless the difference in size of these two populations is small.

Primary Endpoint Analysis and multiplicity adjustment

The testing of the primary and key secondary endpoints is performed at an overall significance level of 0.025 for the one-sided tests and 0.05 for the two-sided tests. The testing strategy is hierarchical in order to control the overall family-wise type I error in the strong sense. The statistical comparisons is carried out in the following hierarchical order:



8/5 BCVA36 = Group means for the change from baseline in BCVA at Week 36 for the 8 mg/5 group and the 2 mg group. Testing Non-inferiority of 8 mg/5 vs 2mg.
8/3 BCVA36 = Group means for the change from baseline in BCVA at Week 36 for the 8 mg/3 group and the 2 mg group. Testing Non-inferiority of 8 mg/3 vs 2mg.
8/3 NumInj64= Conditional distributions for the number of active injections from baseline to Week 64 for the 8 mg/3 group and the 2 mg group.
8/5 NumInj64= Conditional distributions for the number of active injections from baseline to Week 64 for the 8 mg/5 group and the 2 mg group.
8/5 BCVA36 Sup= Group means for the change from baseline in BCVA at Week 36 for the 8 mg/5 group and the 2 mg group. Testing Superiority of 8 mg/5 vs 2mg.
8/3 BCVA36 Sup= Group means for the change from baseline in BCVA at Week 36 for the 8 mg/3 group and the 2 mg group. Testing Superiority of 8 mg/3 vs 2mg.

Figure 7: Hierarchical hypothesis testing

Main statistical approach

For the primary analysis of the primary efficacy variable, a mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate and treatment group (2q4 vs 8q8/3 vs 8q8/5), visit (up to Week 36), and the stratification variables (geographic region [Japan vs. APAC vs Europe vs America], categorized baseline BCVA [<60 vs. ≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors as well as terms for the interaction between baseline and visit (up to Week 36) and for the interaction between treatment and visit (up to Week 36). Only data up to Week 36 were included for this analysis. A Kenward-Roger approximation was used for the denominator degrees of freedom. Further, an unstructured covariance structure was used to model the within subject error, assuming different covariance parameters per treatment group. The unstructured covariance structure was used since it avoids making any assumptions on the correlations between repeated measures. If the fit of the unstructured covariance structure fails to converge, the following covariance structures were tried in order until convergence is reached: Toeplitz with heterogeneity, autoregressive with heterogeneity, Toeplitz, autoregressive and compound symmetry.

With regard to the hierarchy of hypotheses tested, the sponsor prioritizes the non-inferiority with respect to BCVA at 36 weeks of the 8 mg dose with 5 loading doses over the 8 mg/3 modality. The other hypotheses were tested in the following order: non-inferiority regarding BCVA of 8 mg/3 at 36 weeks, superiority regarding the number of injections of 8 mg/3 and 8 mg/5 at 64 weeks, and

superiority at 36 weeks of the two 8 mg doses with respect to BCVA. Failure of one hypothesis will invalidate those that follow.
The Statistical approach for the primary analysis is consistent with the hypothetical strategy handling intercurrent events.
The proposed strategy for the variance-covariance matrices used in statistical model in the event of non-convergence is reasonable and acceptable.

Results

Participant flow

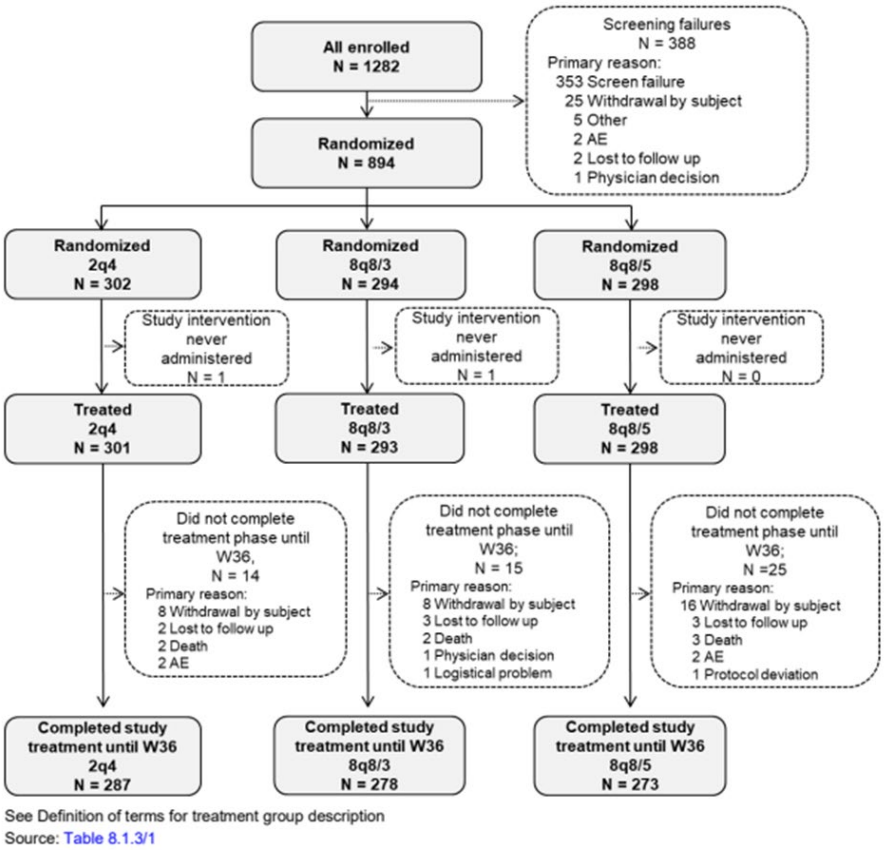


Figure 8: Flow of participants through week 36 (all enrolled participants)

Table 8: Disposition in overall study: week 36 (all randomized participants)

Number of subjects	2q4	8q8/3	8q8/5	All 8 mg	Total
Randomized, n (%)	302 (100.0%)	294 (100.0%)	298 (100.0%)	592 (100.0%)	894 (100.0%)
Treated, n (%)	301 (99.7%)	293 (99.7%)	298 (100.0%)	591 (99.8%)	892 (99.8%)
Completed study until Week 36, n (%)	287 (95.0%)	278 (94.6%)	273 (91.6%)	551 (93.1%)	838 (93.7%)
Did not complete study until Week 36, n (%)	14 (4.6%)	13 (4.4%)	23 (7.7%)	36 (6.1%)	50 (5.6%)[a]
Primary reason					
Withdrawal by subject	8 (2.6%)	8 (2.7%)	16 (5.4%)	24 (4.1%)	32 (3.6%)
Lost to follow-up	2 (0.7%)	2 (0.7%)	2 (0.7%)	4 (0.7%)	6 (0.7%)
Death	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)	7 (0.8%)
Adverse event	2 (0.7%)	0	1 (0.3%)	1 (0.2%)	3 (0.3%)
Protocol deviation	0	0	1 (0.3%)	1 (0.2%)	1 (0.1%)
Physician decision	0	1 (0.3%)	0	1 (0.2%)	1 (0.1%)

Participants who completed the study are those who were followed for the duration of the study, irrespective of permanent discontinuation of study intervention.

a No information was available on whether follow-up was completed or not for 4 participants (2 each in 8q8/3 and 8q8/5 groups) (Table 8.1.3/1)

See Definition of terms for treatment group description

According to the Applicant's results, the number of patients randomized appears well-balanced across treatment groups. However, Table 8 indicates a higher number of patients who did not complete the study until Week 36 in the 8q8/5 group (23, 7.7%) compared to the 8q8/3 group (13, 4.4%) and the

2q4 group (14, 4.6%). This elevated non-completion rate in the 8q8/5 group is primarily due to a higher number of subject withdrawals (16, 5.4%) compared to the 8q8/3 group (8, 2.7%) and the 2q4 group (8, 2.6%).

The Applicant was asked to clarify why a greater proportion of patients in the 8q8/5 group (23 patients, 7.7%) did not complete the study through Week 36, compared with the 8q8/3 group (13 patients, 4.4%) and the 2q4 group (14 patients, 4.6%). This higher discontinuation rate in the 8q8/5 group was mainly driven by subject withdrawals (16 patients, 5.4%) versus 8 patients (2.7%) in the 8q8/3 group and 8 patients (2.6%) in the 2q4 group.

The Applicant emphasized that the reasons for withdrawal did not indicate any consistent trend that could account for the difference. However, analysis of withdrawal timing showed that the largest imbalance occurred within the first three months. In particular, 6 participants in the 8q8/5 group withdrew consent before the scheduled Week 12 injection, compared with only 1 participant in the 8q8/3 group. Since treatment regimens were identical in the 8q8/5 and 8q8/3 groups up to Week 12, this discrepancy is considered most likely due to chance rather than the study drug. Also, withdrawal and overall discontinuation rates remained low across all groups and were within the expected range (<10%).

Further clarification was requested regarding the discrepancy between tables which relate to overall treatment disposition and discontinuation from the study versus discontinuation from study. The Applicant argued that as specified in the Clinical Study Protocol, participants who discontinued treatment were permitted to remain in the study. Consequently, the number of participants who discontinued from the study is lower than the number who discontinued from treatment which correspond to the difference observed. The arguments provided by the Applicant are fully accepted.

Recruitment

Date first subject randomized: **15 May 2023**

Date last subject completed Week 36: 07 Nov 2024 / End of Study Visit Week 64:27 May 2025

Note: At the time of the variation submission, the study was still ongoing and was completed before the end of this procedure.

Conduct of the study

Table 9: Number of participants with important protocol deviations through week 36 (all randomized participants)

Protocol deviation category	2q4 N = 302 (100%)	8q8/3 N = 294 (100%)	8q8/5 N = 298 (100%)	All 8 mg N = 592 (100%)	Total N = 894 (100%)
Subjects with any important deviation, n (%)	45 (14.9%)	63 (21.4%)	60 (20.1%)	123 (20.8%)	168 (18.8%)
AE/SAE [a]	0	3 (1.0%)	2 (0.7%)	5 (0.8%)	5 (0.6%)
EXCLUDED CONCOMITANT MEDICATION TREATMENT	0	0	2 (0.7%)	2 (0.3%)	2 (0.2%)
INCLUSION/EXCLUSION CRITERIA NOT MET BUT SUBJECT ENTERED TREATMENT	2 (0.7%)	6 (2.0%)	11 (3.7%)	17 (2.9%)	19 (2.1%)
INFORMED CONSENT [b]	3 (1.0%)	3 (1.0%)	10 (3.4%)	13 (2.2%)	16 (1.8%)
OTHER PROTOCOL DEVIATIONS	3 (1.0%)	1 (0.3%)	2 (0.7%)	3 (0.5%)	6 (0.7%)
PROCEDURE DEVIATIONS	8 (2.6%)	13 (4.4%)	9 (3.0%)	22 (3.7%)	30 (3.4%)
TREATMENT DEVIATIONS [c]	30 (9.9%)	43 (14.6%)	25 (8.4%)	68 (11.5%)	98 (11.0%)

Participants may have more than one protocol deviation but are only counted once within each deviation category.

(a) Initial SAE was not reported within 24 hours of awareness of event as per the protocol requirement (Listing 10.2.2/1)

(b) The Informed consent form was incomplete (subject's signature/sign date were missing or partially signed or incorrect, etc) in 15 participants. For 1 participant the reason was "the subject signed the informed consent form after starting his/her participation on the study (informed consent date was after the assessment date)"(Listing 10.2.2/1).

(c) The most common reported treatment deviation was related to participants not being extended despite meeting the extension criteria (reference to Listing 10.2.2/1).

See Definition of terms for treatment group description.

Table 10: Number of participants with important protocol deviations through week 64 (all randomized participants)

Protocol deviation category	2q4 N = 302 (100%)	8q8/3 N = 294 (100%)	8q8/5 N = 298 (100%)	All 8 mg N = 592 (100%)	Total N = 894 (100%)
Subjects with any important deviation, n (%)	85 (28.1%)	90 (30.6%)	100 (33.6%)	190 (32.1%)	275 (30.8%)
AE/SAE [a]	0	4 (1.4%)	6 (2.0%)	10 (1.7%)	10 (1.1%)
EXCLUDED CONCOMITANT MEDICATION TREATMENT	0	0	2 (0.7%)	2 (0.3%)	2 (0.2%)
INCLUSION/EXCLUSION CRITERIA NOT MET BUT SUBJECT ENTERED TREATMENT	5 (1.7%)	8 (2.7%)	13 (4.4%)	21 (3.5%)	26 (2.9%)
INFORMED CONSENT	3 (1.0%)	4 (1.4%)	10 (3.4%)	14 (2.4%)	17 (1.9%)
OTHER PROTOCOL DEVIATIONS	4 (1.3%)	3 (1.0%)	3 (1.0%)	6 (1.0%)	10 (1.1%)
PROCEDURE DEVIATIONS	18 (6.0%)	31 (10.5%)	28 (9.4%)	59 (10.0%)	77 (8.6%)
TREATMENT DEVIATIONS [b]	62 (20.5%)	62 (21.1%)	52 (17.4%)	114 (19.3%)	176 (19.7%)

Participants may have more than one protocol deviation but are only counted once within each deviation category.

(a) Delay in reporting of AEs of special interest and SAEs as per protocol (Listing 10.2.2/1)

(b) The most common reported treatment deviation was related to participants not being extended despite meeting the extension criteria (Listing 10.2.2/1).

See Definition of terms for treatment group description.

A total of 168 participants (18.8%) experienced major protocol deviations. The most common deviations (≥5%) were related to treatment. Based on the data provided by the Applicant, a higher number of important protocol deviations was observed in the 8q8/3 group (63 patients, 21.4%) and the 8q8/5 group (60 patients, 20.1%) compared to the 2q4 group (45 patients, 14.9%).

When analyzing the different categories of major deviations, most appear to be relatively balanced across the treatment groups — except for treatment-related deviations. Notably, treatment deviations occurred more frequently in the 8q8/3 group (43 patients, 14.6%) compared to the 2q4 and 8q8/5 groups (30 patients [9.9%] and 25 patients [8.4%], respectively).

According to table 10, the most common reported treatment deviation was related to participants not being extended despite meeting the extension criteria.

The Applicant was asked to clarify why the most commonly reported treatment deviation involved participants who were not extended despite meeting the extension criteria, and in particular, to explain why such deviations occurred more frequently in the 8q8/3 group.

The Applicant emphasized that, according to the dosing schedule outlined in the Clinical Study Protocol, participants in the 8q8/3 and 2q4 groups were allowed to extend their dosing intervals starting at Week 32, whereas participants in the 8q8/5 group were not permitted to do so until Week 40. Consequently, a protocol deviation involving interval extensions through Week 36 could only occur in the 8q8/3 and 2q4 groups, and not in the 8q8/5 group.

Moreover, according to the data provided by the Applicant, participants in the 8q8/3 and 2q4 groups who met the criteria but were not extended showed a balanced distribution between the two groups (19 vs. 16 participants).

Also, according to the data provided by the Applicant at Week 64, the treatment deviations are well balanced between each group of treatment (2q4, 8q8/3, 8q8/5) with a slight higher frequency concerning the 2q4 group (62 patients, 20,5%) and the group 8q8/3 (62 patients, 21.1%) compared to the 8q8/5 group (52 patients, 17.4%).

While it is clear that the sponsor followed the recommendations of ICH E9-R1, the request for this additional sensitivity analysis was made in order to obtain a more comprehensive overview of the diversity of exposure patterns among patients included in the trial.

It is agreed that the hypothetical strategy proposed in the main analysis is preferable to the treatment policy strategy in a non-inferiority context, as the population considered in the latter strategy has greater variability, which may make the treatment arms more similar. However, the population considered in the proposed hypothetical strategy, because it includes major deviations from the protocol, still retains a degree of variability that could nonetheless favour the similarity of the treatment arms in terms of point estimates. In addition, the size of this population may also have an impact on the accuracy of estimates and the sensitivity of statistical tests.

Nevertheless, the sponsor provided the requested analysis on the population that adhered most closely to the protocol. It shows a very limited impact on the initial results, with a loss of one letter in terms of point estimates and precision (lower limit of the 95% CI) which does not jeopardize the non-inferiority of the new treatment modalities (8q8/3 and 8q8/5) compared to the control modality (2q4) and fully supports the robustness of the primary analysis conclusion.

Full analysis set (N=892)

Contrast [b]	8q8/3 -2q4	8q8/5 -2q4
Estimate for contrast and two-sided 95% CI [c]	-0.1 (-2.0, 1.9)	0.8 (-1.1, 2.7)
p-value of one-sided test for non-inferiority at a margin of 4 letters	<.0001	<.0001

Per-protocole analysis set (N=726)

Contrast [b]	8q8/3 -2q4	8q8/5 -2q4
Estimate for contrast and two-sided 95% CI [c]	-1.2 (-3.2, 0.9)	-0.3 (-2.4, 1.8)
p-value of one-sided test for non-inferiority at a margin of 4 letters	0.0036	0.0003

Amendment to the protocol history

- **Amendment 1.0 (28 JUL 2023)**

This amendment has been prepared to incorporate country-specific modifications to the original

protocol dated 07 February 2023, in order to comply with local requirements applicable solely to countries under the EU Clinical Trial Regulation (EU CTR). In accordance with the criteria outlined in Article 10(a) of Directive 2001/20/EC of the European Parliament and of the Council, this amendment is considered non-substantial.

Baseline data

Table 11: Demographics and disease characteristics (full analysis set)

	2q4 N = 301 (100%)	8q8/3 N = 293 (100%)	8q8/5 N = 298 (100%)	All 8 mg N = 591 (100%)	Total N = 892 (100%)
Sex, n (%)					
Female	144 (47.8%)	136 (46.4%)	146 (49.0%)	282 (47.7%)	426 (47.8%)
Male	157 (52.2%)	157 (53.6%)	152 (51.0%)	309 (52.3%)	466 (52.2%)
Race, n (%)					
American Indian or Alaska Native	0	0	2 (0.7%)	2 (0.3%)	2 (0.2%)
Asian	101 (33.6%)	91 (31.1%)	97 (32.6%)	188 (31.8%)	289 (32.4%)
Black or African American	8 (2.7%)	7 (2.4%)	9 (3.0%)	16 (2.7%)	24 (2.7%)
Multiple	1 (0.3%)	0	1 (0.3%)	1 (0.2%)	2 (0.2%)
Native Hawaiian or other Pacific Islander	0	0	1 (0.3%)	1 (0.2%)	1 (0.1%)
Not reported	13 (4.3%)	22 (7.5%)	11 (3.7%)	33 (5.6%)	46 (5.2%)
White	178 (59.1%)	173 (59.0%)	177 (59.4%)	350 (59.2%)	528 (59.2%)
Ethnicity, n (%)					
Hispanic or Latino	22 (7.3%)	25 (8.5%)	14 (4.7%)	39 (6.6%)	61 (6.8%)
Not Hispanic or Latino	267 (88.7%)	254 (86.7%)	273 (91.6%)	527 (89.2%)	794 (89.0%)
Not reported	12 (4.0%)	14 (4.8%)	11 (3.7%)	25 (4.2%)	37 (4.1%)
Age at enrollment (years)					
n	301	293	298	591	892
Mean (SD)	65.9 (11.7)	65.8 (11.5)	65.8 (11.5)	65.8 (11.5)	65.9 (11.6)
Median (Min, Max)	67.0 (27, 89)	67.0 (23, 95)	66.0 (38, 92)	67.0 (23, 95)	67.0 (23, 95)
Age group (years), n (%)					
<55	47 (15.6%)	54 (18.4%)	53 (17.8%)	107 (18.1%)	154 (17.3%)
≥55 to <65	78 (25.9%)	71 (24.2%)	75 (25.2%)	146 (24.7%)	224 (25.1%)
≥65 to <75	103 (34.2%)	92 (31.4%)	96 (32.2%)	188 (31.8%)	291 (32.6%)
≥75	73 (24.3%)	76 (25.9%)	74 (24.8%)	150 (25.4%)	223 (25.0%)
Body mass index (kg/m²)					
n	300	291	294	585	885
Mean (SD)	27.40 (5.53)	27.55 (5.11)	27.61 (5.02)	27.58 (5.06)	27.52 (5.22)
Median (Min, Max)	27.00 (14.8, 60.8)	27.00 (16.4, 43.3)	27.10 (14.9, 48.6)	27.00 (14.9, 48.6)	27.00 (14.8, 60.8)
Systolic blood pressure (mmHg)					
n	301	293	298	591	892
Mean (SD)	135.38 (11.45)	135.22 (11.74)	134.76 (11.83)	134.99 (11.78)	135.12 (11.66)
Median (Min, Max)	135.50 (98.0, 160.0)	135.50 (98.0, 158.5)	134.50 (105.5, 177.0)	135.00 (98.0, 177.0)	135.00 (98.0, 177.0)
Diastolic blood pressure (mmHg)					
n	301	293	298	591	892
Mean (SD)	79.36 (7.74)	79.76 (8.16)	79.98 (8.01)	79.87 (8.08)	79.70 (7.97)
Median (Min, Max)	80.50 (57.0, 96.5)	80.00 (53.0, 96.0)	80.50 (56.0, 99.0)	80.50 (53.0, 99.0)	80.50 (53.0, 99.0)

	2q4 N = 301 (100%)	8q8/3 N = 293 (100%)	8q8/5 N = 298 (100%)	All 8 mg N = 591 (100%)	Total N = 892 (100%)
Prior fellow eye treatment, n (%)					
Yes	3 (1.0%)	1 (0.3%)	2 (0.7%)	3 (0.5%)	6 (0.7%)
Aflibercept	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.2%)
Bevacizumab	2 (0.7%)	0	2 (0.7%)	2 (0.3%)	4 (0.4%)
Ranibizumab	1 (0.3%)	0	0	0	1 (0.1%)
Medical history of hypertension, n (%)					
Yes	187 (62.1%)	192 (65.5%)	196 (65.8%)	388 (65.7%)	575 (64.5%)
Medical history of diabetes, n (%)					
Yes	61 (20.3%)	53 (18.1%)	52 (17.4%)	105 (17.8%)	166 (18.6%)
Medical history of cerebrovascular disease, n (%)					
Yes	19 (6.3%)	25 (8.5%)	15 (5.0%)	40 (6.8%)	59 (6.6%)
Medical history of ischaemic heart disease, n (%)					
Yes	28 (9.3%)	22 (7.5%)	23 (7.7%)	45 (7.6%)	73 (8.2%)
Medical history of renal impairment, n (%)					
Normal	180 (59.8%)	193 (65.9%)	196 (65.8%)	389 (65.8%)	569 (63.8%)
Mild	94 (31.2%)	75 (25.6%)	76 (25.5%)	151 (25.5%)	245 (27.5%)
Moderate	16 (5.3%)	16 (5.5%)	17 (5.7%)	33 (5.6%)	49 (5.5%)
Severe	3 (1.0%)	3 (1.0%)	5 (1.7%)	8 (1.4%)	11 (1.2%)
Missing	8 (2.7%)	6 (2.0%)	4 (1.3%)	10 (1.7%)	18 (2.0%)
Medical history of hepatic impairment, n (%)					
No	288 (95.7%)	278 (94.9%)	287 (96.3%)	565 (95.6%)	853 (95.6%)
Yes	13 (4.3%)	15 (5.1%)	11 (3.7%)	26 (4.4%)	39 (4.4%)
NEI-VFQ-25 total score					
n	301	293	298	591	892
Mean (SD)	78.979 (15.816)	79.395 (15.014)	78.148 (16.027)	78.766 (15.532)	78.838 (15.620)
Median	82.880	82.420	83.095	82.730	82.840
(Min, Max)	(23.04, 100.00)	(32.33, 100.00)	(21.82, 100.00)	(21.82, 100.00)	(21.82, 100.00)

NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25.
Multiple: Participants who reported that they belong to more than one race.
See Definition of terms for treatment group description.

Overall, there were no significant differences in demographics or baseline characteristics between the various types of RVO (BRVO and CRVO/HRVO), aside from minor variations in sex, race, and history of diabetes or renal impairment, which were not deemed clinically relevant.

The following differences (>5%) were observed by RVO type:

- A higher proportion of female participants was noted in the BRVO group compared to the CRVO/HRVO group (53.1% vs 41.9%, respectively).
- Participants of Asian race were more frequently represented in the BRVO group than in the CRVO/HRVO group (38.8% vs 25.4%, respectively).
- A greater proportion of participants with a medical history of normal renal function was reported in the BRVO group compared to the CRVO/HRVO group (67.9% vs 59.3%, respectively).
- The proportion of participants with a history of diabetes was lower in the BRVO group than in the CRVO/HRVO group (12.6% vs 25.2%, respectively).

Proportion of male and female was well balanced between the 3 arms, even if slightly more male patients were included in total (52.2%). Data were mostly well balanced across the treatment groups for the demographics and disease characteristics at baseline, except for discrepancies observed between groups in patients with medical history of renal impairment (normal and mild). Moreover, the mean age observed in QUASAR, VIBRANT, GALILEO and COPERNICUS appears to be similar, overall 65 years old.

Furthermore, the characteristics observed for the various types of RVO (BRVO and CRVO/HRVO), seem to be well balanced.

Baseline disease characteristics of the study eye

Table 12: Baseline disease characteristics of the study eye (full analysis set)

	2q4 N = 301 (100%)	8q8/3 N = 293 (100%)	8q8/5 N = 298 (100%)	All 8 mg N = 591 (100%)	Total N = 892 (100%)
RVO type[a]					
BRVO	149 (49.5%)	159 (54.3%)	159 (53.4%)	318 (53.8%)	467 (52.4%)
CRVO	117 (38.9%)	99 (33.8%)	102 (34.2%)	201 (34.0%)	318 (35.7%)
HRVO	35 (11.6%)	35 (11.9%)	37 (12.4%)	72 (12.2%)	107 (12.0%)
RVO Type (used for stratified randomization)[b]					
BRVO	174 (57.8%)	172 (58.7%)	175 (58.7%)	347 (58.7%)	521 (58.4%)
CRVO / HRVO	127 (42.2%)	121 (41.3%)	123 (41.3%)	244 (41.3%)	371 (41.6%)
BCVA (ETDRS letters score)					
n	301	293	298	591	892
Mean (SD)	54.1 (14.3)	55.2 (13.6)	55.4 (13.4)	55.3 (13.5)	54.9 (13.8)
Median (min, max)	58.0 (24, 73)	57.0 (24, 73)	58.0 (18, 74)	58.0 (18, 74)	58.0 (18, 74)
Categorized BCVA (ETDRS letters score), n (%)					
<60	166 (55.1%)	163 (55.6%)	168 (56.4%)	331 (56.0%)	497 (55.7%)
≥60	135 (44.9%)	130 (44.4%)	130 (43.6%)	260 (44.0%)	395 (44.3%)
Intraocular pressure (mmHg)					
n	301	293	298	591	892
Mean (SD)	14.6 (3.1)	14.7 (3.1)	14.7 (3.0)	14.7 (3.1)	14.7 (3.1)
Median (min, max)	14.0 (6, 24)	15.0 (7, 24)	14.0 (7, 26)	15.0 (7, 26)	14.5 (6, 26)
CST (µm)					
n	300	293	298	591	891
Mean (SD)	651.0 (240.0)	626.1 (230.2)	609.2 (213.3)	617.6 (221.8)	628.8 (228.5)
Median (min, max)	603.5 (302, 1601)	575.0 (272, 1499)	569.0 (268, 1424)	574.0 (268, 1499)	581.0 (268, 1601)
Presence of perifoveal and parafoveal ischemia by FA, n (%)					
No	72 (23.9%)	56 (19.1%)	62 (20.8%)	118 (20.0%)	190 (21.3%)
Yes	178 (59.1%)	199 (67.9%)	185 (62.1%)	384 (65.0%)	562 (63.0%)
undetermined	28 (9.3%)	24 (8.2%)	29 (9.7%)	53 (9.0%)	81 (9.1%)
missing	23 (7.6%)	14 (4.8%)	22 (7.4%)	36 (6.1%)	59 (6.6%)
Total area of macular ischemia (not considering the FAZ) by FA (mm^2)					
n	257	247	250	497	754
Mean (SD)	4.204 (4.804)	4.681 (4.831)	4.643 (4.909)	4.662 (4.866)	4.506 (4.847)
Median (min, max)	2.900 (0.00, 28.08)	3.910 (0.00, 26.86)	3.255 (0.00, 24.20)	3.810 (0.00, 26.86)	3.300 (0.00, 28.08)
Presence of retinal areas of non-perfusion outside the macula by FA, n (%)					
No	72 (23.9%)	67 (22.9%)	64 (21.5%)	131 (22.2%)	203 (22.8%)
Yes	189 (62.8%)	197 (67.2%)	193 (64.8%)	390 (66.0%)	579 (64.9%)
undetermined	27 (9.0%)	18 (6.1%)	28 (9.4%)	46 (7.8%)	73 (8.2%)
missing	13 (4.3%)	11 (3.8%)	13 (4.4%)	24 (4.1%)	37 (4.1%)

BCVA = Best corrected visual acuity, BRVO = branch retinal vein occlusion, CRVO = central retinal vein occlusion, CST = Central subfield thickness, ETDRS = Early treatment diabetic retinopathy study, FA = Fluorescein angiography, FAZ = Foveal avascular zone, HRVO = hemiretinal vein occlusion, RVO = retinal vein occlusion.
(a) RVO type based on reading center assessment (investigator assessment is used for participants with missing reading center data).
(b) RVO type based on investigator assessment; used for strata assignment at randomization via the IxRS system.
See Definition of terms for treatment group description.

At baseline, the mean (SD) BCVA using the ETDRS letter score, averaged across all treatment groups, was 54.9 (13.8) letters. A total of 55.7% of participants had an ETDRS score of <60 letters, while 44.3% had a score of ≥60 letters. The mean (SD) intraocular pressure in the study eye at baseline was 14.7 (3.1) mmHg, and the mean (SD) central subfield thickness (CST) was 628.8 (228.5) µm.

The following differences (>5%) were noted between treatment groups:

- CRVO type based on reading center assessment was slightly more prevalent in the 2q4 group (38.9% participants) compared to the 8q8/3 and 8q8/5 groups (33.8% and 34.2%, respectively). However, RVO types were well balanced across all treatment groups when using investigator assessment for strata assignment at randomization.
- Most participants in all treatment groups had perifoveal and parafoveal ischemia by FA, although there were slightly less in the 2q4 group compared to the "All 8 mg" group (59.1% vs 65.0%, respectively).
- The mean values of CST at baseline were slightly higher in the 2q4 group (651.0 µm) compared to 8q8/3 and 8q8/5 groups (626.1 and 609.2 µm, respectively).

Table 13: Baseline disease characteristics of the study eye by RVO type (full analysis set)

RVO Type: CRVO/HRVO	2q4 N=152 (100%)	8q8/3 N=134 (100%)	8q8/5 N=139 (100%)	All 8mg N=273 (100%)	Total N=425 (100%)
RVO Type (a)					
BRVO	0	0	0	0	0
CRVO	117 (77.0%)	99 (73.9%)	102 (73.4%)	201 (73.6%)	318 (74.8%)
HRVO	35 (23.0%)	35 (26.1%)	37 (26.6%)	72 (26.4%)	107 (25.2%)
RVO Type (used for stratified randomization) (b)					
BRVO	29 (19.1%)	20 (14.9%)	21 (15.1%)	41 (15.0%)	70 (16.5%)
CRVO / HRVO	123 (80.9%)	114 (85.1%)	118 (84.9%)	232 (85.0%)	355 (83.5%)
BCVA (ETDRS letters score)					
n	152	134	139	273	425
Mean (SD)	51.0 (14.7)	51.3 (14.8)	51.8 (14.5)	51.5 (14.6)	51.3 (14.7)
Median	54.0	52.5	55.0	54.0	54.0
Q1, Q3	40.0, 62.5	40.0, 63.0	40.0, 63.0	40.0, 63.0	40.0, 63.0
Min, Max	24, 73	24, 73	18, 74	18, 74	18, 74
Categorized BCVA (ETDRS letters score)					
< 60	98 (64.5%)	88 (65.7%)	95 (68.3%)	183 (67.0%)	281 (66.1%)
>= 60	54 (35.5%)	46 (34.3%)	44 (31.7%)	90 (33.0%)	144 (33.9%)
Intraocular pressure (mmHg)					
n	152	134	139	273	425
Mean (SD)	14.8 (3.2)	15.0 (3.0)	14.8 (3.0)	14.9 (3.0)	14.8 (3.1)
Median	15.0	15.0	15.0	15.0	15.0
Q1, Q3	13.0, 17.0	13.0, 17.0	13.0, 17.0	13.0, 17.0	13.0, 17.0
Min, Max	6, 24	7, 23	7, 26	7, 26	6, 26
Central subfield thickness (CST) (um)					
n	151	134	139	273	424
Mean (SD)	748.0 (259.5)	717.9 (257.4)	687.7 (237.7)	702.5 (247.6)	718.7 (252.5)
Median	700.0	683.5	654.0	676.0	690.5
Q1, Q3	573.0, 892.0	535.0, 858.0	491.0, 868.0	502.0, 858.0	525.5, 869.0
Min, Max	316, 1601	305, 1499	313, 1424	305, 1499	305, 1601
Categorized CST (Central subfield thickness)					
missing	1 (0.7%)	0	0	0	1 (0.2%)
<= Observed Median (581 um)	41 (27.0%)	46 (34.3%)	56 (40.3%)	102 (37.4%)	143 (33.6%)
> Observed Median (581 um)	110 (72.4%)	88 (65.7%)	83 (59.7%)	171 (62.6%)	281 (66.1%)
Presence of perifoveal and parafoveal ischemia by FA					
missing	12 (7.9%)	5 (3.7%)	14 (10.1%)	19 (7.0%)	31 (7.3%)
No	63 (41.4%)	47 (35.1%)	55 (39.6%)	102 (37.4%)	165 (38.8%)
Undetermined	20 (13.2%)	15 (11.2%)	17 (12.2%)	32 (11.7%)	52 (12.2%)
Yes	57 (37.5%)	67 (50.0%)	53 (38.1%)	120 (44.0%)	177 (41.6%)
Total area of macular ischemia (not considering the FAZ) by FA (mm2)					
n	129	114	113	227	356
Mean (SD)	2.470 (5.099)	3.609 (5.677)	2.996 (5.399)	3.304 (5.537)	3.002 (5.390)
Median	0.000	0.000	0.000	0.000	0.000
Q1, Q3	0.000, 2.280	0.000, 6.400	0.000, 4.120	0.000, 5.460	0.000, 4.700
Min, Max	0.00, 28.08	0.00, 26.86	0.00, 24.20	0.00, 26.86	0.00, 28.08
Presence of retinal areas of non-perfusion outside the macula by FA					
missing	9 (5.9%)	8 (6.0%)	11 (7.9%)	19 (7.0%)	28 (6.6%)
No	39 (25.7%)	35 (26.1%)	39 (28.1%)	74 (27.1%)	113 (26.6%)
Undetermined	19 (12.5%)	15 (11.2%)	20 (14.4%)	35 (12.8%)	54 (12.7%)
Yes	85 (55.9%)	76 (56.7%)	69 (49.6%)	145 (53.1%)	230 (54.1%)

BCVA = Best corrected visual acuity; BRVO = Branch retinal vein occlusion; CRVO = Central retinal vein occlusion; ETDRS = Early treatment diabetic retinopathy study; FA = Fluorescein angiography assessment; FAZ = Foveal avascular zone; HRVO = Hemiretinal vein occlusion; RVO = Retinal vein occlusion
(a) RVO type based on reading center assessment (investigator assessment is used for participnts with missing reading center data).
(b) RVO type based on investigator assessment; used for strata assignment at randomization via the IxRS system.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.
All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals.

The data were generally well balanced across treatment groups. The disparity in baseline CST between (BRVO) and (CRVO/HRVO) can well be attributed to the distinct pathophysiological mechanisms underlying these conditions. CRVO/HRVO involves a more extensive occlusion of venous outflow compared to BRVO, typically presenting with higher oedema and consequently higher CST values on (OCT) scans.

Medical and surgical history

Table 14: Ocular medical history finding in the study eye (15 most frequent preferred terms in each treatment group)

Primary system organ class Preferred term MedDRA version 27.0	2q4 N = 301 (100%)	8q8/3 N = 293 (100%)	8q8/5 N = 298 (100%)	All 8 mg N = 591 (100%)	Total N = 892 (100%)
Number (%) of participants with at least one medical history finding, n (%)	301 (100.0%)	291 (99.3%)	298 (100.0%)	589 (99.7%)	890 (99.8%)
Eye disorders	301 (100.0%)	290 (99.0%)	297 (99.7%)	587 (99.3%)	888 (99.6%)
Retinal vein occlusion	285 (94.7%)	275 (93.9%)	285 (95.6%)	560 (94.8%)	845 (94.7%)
Cataract	148 (49.2%)	146 (49.8%)	143 (48.0%)	289 (48.9%)	437 (49.0%)
Macular oedema	40 (13.3%)	37 (12.6%)	36 (12.1%)	73 (12.4%)	113 (12.7%)
Vitreous detachment	36 (12.0%)	33 (11.3%)	32 (10.7%)	65 (11.0%)	101 (11.3%)
Cataract nuclear	35 (11.6%)	28 (9.6%)	25 (8.4%)	53 (9.0%)	88 (9.9%)
Dry eye	20 (6.6%)	24 (8.2%)	19 (6.4%)	43 (7.3%)	63 (7.1%)
Retinopathy hypertensive	19 (6.3%)	22 (7.5%)	18 (6.0%)	40 (6.8%)	59 (6.6%)
Retinal haemorrhage	17 (5.6%)	15 (5.1%)	19 (6.4%)	34 (5.8%)	51 (5.7%)
Cystoid macular oedema	25 (8.3%)	15 (5.1%)	17 (5.7%)	32 (5.4%)	57 (6.4%)
Pseudophakia	13 (4.3%)	11 (3.8%)	14 (4.7%)	25 (4.2%)	38 (4.3%)
Glaucoma	16 (5.3%)	13 (4.4%)	11 (3.7%)	24 (4.1%)	40 (4.5%)
Vitreous floaters	7 (2.3%)	10 (3.4%)	7 (2.3%)	17 (2.9%)	24 (2.7%)
Epiretinal membrane	7 (2.3%)	6 (2.0%)	8 (2.7%)	14 (2.4%)	21 (2.4%)
Open angle glaucoma	7 (2.3%)	9 (3.1%)	4 (1.3%)	13 (2.2%)	20 (2.2%)
Retinal degeneration	7 (2.3%)	3 (1.0%)	10 (3.4%)	13 (2.2%)	20 (2.2%)
Surgical and medical procedures	40 (13.3%)	40 (13.7%)	44 (14.8%)	84 (14.2%)	124 (13.9%)
Cataract operation	26 (8.6%)	33 (11.3%)	37 (12.4%)	70 (11.8%)	96 (10.8%)
Intraocular lens implant	7 (2.3%)	9 (3.1%)	7 (2.3%)	16 (2.7%)	23 (2.6%)

MedDRA = Medical Dictionary for Regulatory Activities
A participant was counted only once within each primary system organ class/preferred term.
The 15 most frequent preferred terms in each treatment group and their associated system organ class are sorted by decreasing order of frequency in the total group.
See Definition of terms for treatment group description.

Table 15: Non-ocular medical history findings (15 most frequent preferred terms in each treatment group)

Primary system organ class Preferred term MedDRA version 27.#	2q4 N = 301 (100%)	8q8/3 N = 293 (100%)	8q8/5 N = 298 (100%)	All 8 mg N = 591 (100%)	Total N = 892 (100%)
Number (%) of subjects with at least one medical history finding, n (%)	264 (87.7%)	270 (92.2%)	282 (94.6%)	552 (93.4%)	816 (91.5%)
Vascular disorders	186 (61.8%)	190 (64.8%)	196 (65.8%)	386 (65.3%)	572 (64.1%)
Hypertension	173 (57.5%)	180 (61.4%)	186 (62.4%)	366 (61.9%)	539 (60.4%)
Metabolism and nutrition disorders	149 (49.5%)	138 (47.1%)	146 (49.0%)	284 (48.1%)	433 (48.5%)
Hypercholesterolaemia	43 (14.3%)	57 (19.5%)	55 (18.5%)	112 (19.0%)	155 (17.4%)
Hyperlipidaemia	47 (15.6%)	43 (14.7%)	37 (12.4%)	80 (13.5%)	127 (14.2%)
Type 2 diabetes mellitus	39 (13.0%)	27 (9.2%)	30 (10.1%)	57 (9.6%)	96 (10.8%)
Dyslipidaemia	14 (4.7%)	18 (6.1%)	18 (6.0%)	36 (6.1%)	50 (5.6%)
Diabetes mellitus	12 (4.0%)	22 (7.5%)	13 (4.4%)	35 (5.9%)	47 (5.3%)
Surgical and medical procedures	89 (29.6%)	93 (31.7%)	95 (31.9%)	188 (31.8%)	277 (31.1%)
Hysterectomy	18 (6.0%)	17 (5.8%)	17 (5.7%)	34 (5.8%)	52 (5.8%)
Musculoskeletal and connective tissue disorders	88 (29.2%)	80 (27.3%)	84 (28.2%)	164 (27.7%)	252 (28.3%)
Osteoarthritis	24 (8.0%)	25 (8.5%)	25 (8.4%)	50 (8.5%)	74 (8.3%)
Arthritis	18 (6.0%)	12 (4.1%)	14 (4.7%)	26 (4.4%)	44 (4.9%)
Osteoporosis	19 (6.3%)	11 (3.8%)	11 (3.7%)	22 (3.7%)	41 (4.6%)
Gastrointestinal disorders	62 (20.6%)	56 (19.1%)	58 (19.5%)	114 (19.3%)	176 (19.7%)
Gastrooesophageal reflux disease	35 (11.6%)	32 (10.9%)	29 (9.7%)	61 (10.3%)	96 (10.8%)
Psychiatric disorders	59 (19.6%)	50 (17.1%)	54 (18.1%)	104 (17.6%)	163 (18.3%)
Depression	20 (6.6%)	23 (7.8%)	22 (7.4%)	45 (7.6%)	65 (7.3%)
Anxiety	26 (8.6%)	20 (6.8%)	12 (4.0%)	32 (5.4%)	58 (6.5%)
Respiratory, thoracic and mediastinal disorders	42 (14.0%)	36 (12.3%)	50 (16.8%)	86 (14.6%)	128 (14.3%)
Asthma	16 (5.3%)	14 (4.8%)	11 (3.7%)	25 (4.2%)	41 (4.6%)
Reproductive system and breast disorders	36 (12.0%)	31 (10.6%)	39 (13.1%)	70 (11.8%)	106 (11.9%)
Benign prostatic hyperplasia	20 (6.6%)	17 (5.8%)	16 (5.4%)	33 (5.6%)	53 (5.9%)
Immune system disorders	25 (8.3%)	35 (11.9%)	31 (10.4%)	66 (11.2%)	91 (10.2%)
Seasonal allergy	18 (6.0%)	25 (8.5%)	16 (5.4%)	41 (6.9%)	59 (6.6%)
Endocrine disorders	35 (11.6%)	21 (7.2%)	25 (8.4%)	46 (7.8%)	81 (9.1%)
Hypothyroidism	25 (8.3%)	14 (4.8%)	14 (4.7%)	28 (4.7%)	53 (5.9%)
Social circumstances	23 (7.6%)	23 (7.8%)	21 (7.0%)	44 (7.4%)	67 (7.5%)
Postmenopause	16 (5.3%)	10 (3.4%)	9 (3.0%)	19 (3.2%)	35 (3.9%)

MedDRA = Medical Dictionary for Regulatory Activities

The 15 most frequent preferred terms in each treatment group and their associated system organ class are sorted by decreasing order of frequency in the total group.

A participant was counted only once within each primary system organ class preferred term.

See Definition of terms for treatment group description.

Regarding ocular history, the most common eye disorders were RVO (94.7%, 93.9%, and 95.6% in the 2q4, 8q8/3 and 8q8/5 groups respectively) and Cataract (49.2%, 49.8%, and 48% in the 2q4, 8q8/3 and 8q8/5 groups respectively), with previous cataract surgery having occurred in 8.6%, 11.3% and 12.4% of subjects in the 2q4, 8q8/3 and 8q8/5 groups respectively.

For non-ocular history, the most common disorders were vascular disorders, especially hypertension and also metabolism and nutrition disorders (hypercholesterolemia, hyperlipidaemia, type 2 diabetes mellitus, dyslipidaemia, and diabetes mellitus).

Overall, the ocular and non-ocular medical and surgical history findings were consistent with what is typically observed in CRVO and an elderly patient population and were largely similar across treatment groups.

Outcomes and estimation

– Primary efficacy endpoint

○ *BCVA change from baseline at week 36*

Table 16: QUASAR: BCVA change from baseline at Week 36 in the study eye

BCVA measured by the ETDRS letter score, MMRM (full analysis set)

	2q4 N = 301	8q8/3 N = 293	8q8/5 N = 298
Baseline mean [a]	54.1	55.2	55.4
Number of participants with Week 36 data (included/excluded due to ICE)	264/17	260/12	248/18
Arithmetic mean (SD) change from baseline [a]	17.8 (13.1)	17.0 (11.8)	19.1 (11.2)
LS mean (SE) change from baseline	17.5 (0.7)	17.4 (0.7)	18.3 (0.6)
Contrast [b]		8q8/3 -2q4	8q8/5 -2q4
Estimate for contrast and two-sided 95% CI [c]		-0.1 (-2.0, 1.9)	0.8 (-1.1, 2.7)
p-value of one-sided test for non-inferiority at a margin of 4 letters		<.0001	<.0001

APAC = Asia-Pacific; BCVA = best-corrected visual acuity; CI = Confidence Interval; ETDRS = early treatment diabetic retinopathy study; ICE = intercurrent event; LS = least squares; MMRM = mixed model for repeated measurements; RVO = retinal vein occlusion; SD = Standard Deviation; SE = Standard Error.

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

ICEs were handled according to primary estimand strategy as described in Module 5.3.5.1 QUASAR W36 CSR, Section 10.1.9, Table 4-2 in SAP Section 4.2.2.1.

(a) based on observed cases excluding data after ICE.

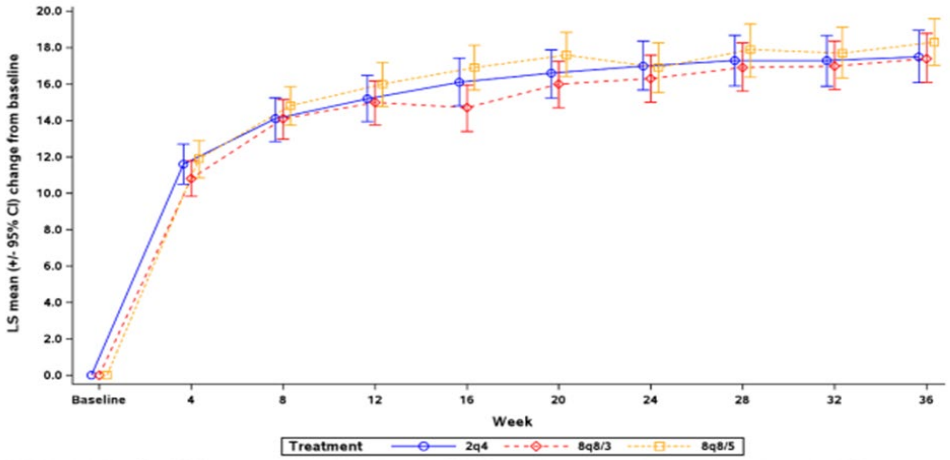
(b) The contrast also includes the interaction term for treatment x visit (at Week 36, for details on the population-level summary see Module 5.3.5.1 QUASAR W36 CSR, Section 10.1.9, SAP Section 4.2.2).

(c) Estimate based on the MMRM, was computed for the differences of 8q8/3 minus 2q4 and 8q8/5 minus 2q4, respectively with two-sided 95% CIs.

See Definition of terms for treatment group description.

Figure 9: QUASAR: BCVA change from baseline

LS mean change from baseline in BCVA measured by the ETDRS letter score in study eye by visit through Week 36, MMRM (full analysis set)



APAC = Asia-Pacific; BCVA = best-corrected visual acuity; ETDRS = early treatment diabetic retinopathy study; ICE = intercurrent events; LS mean = least-squares; MMRM = mixed model for repeated measurements; RVO = retinal vein occlusion;

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

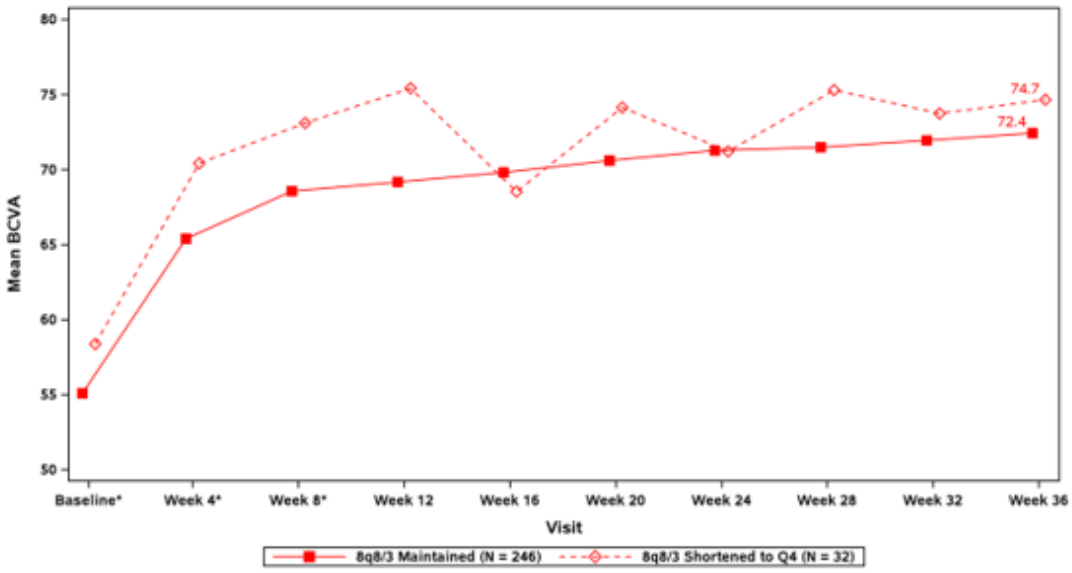
ICEs were handled according to the primary estimand strategy as described in Module 5.3.5.1 QUASAR W36 CSR, Section 10.1.9, Table 4-2.

See Definition of terms for treatment group description.

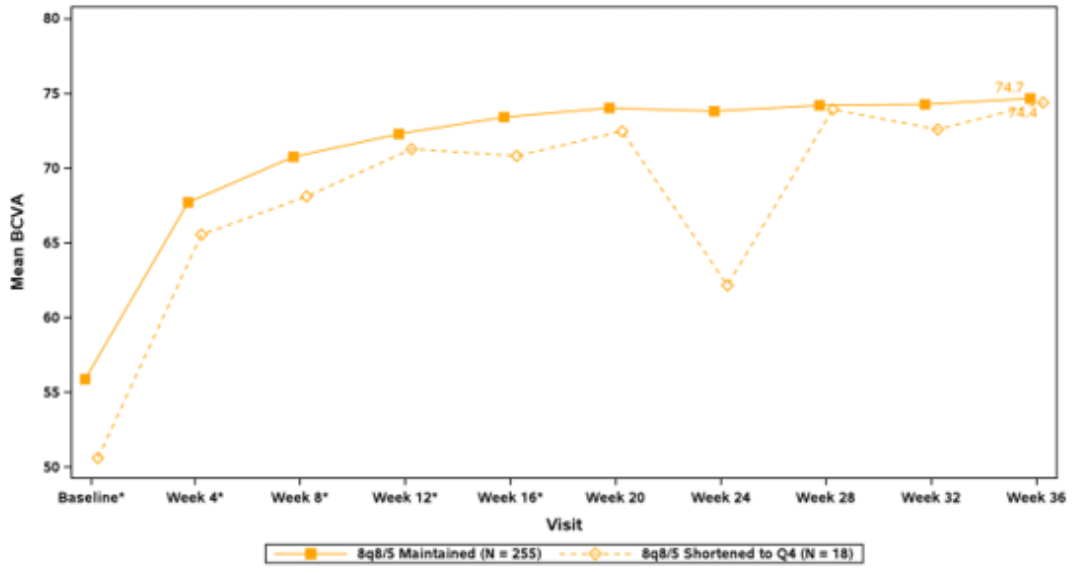
Figure 10: QUASAR: BCVA through week 36 for participants on Q8 versus Q4 intervals

Mean BCVA (ETDRS Letters) by visit through Week 36 in the 8q8/3 (a) and 8q8/5 (b) groups in QUASAR participants who maintained a Q8 interval versus those whose interval was shortened to Q4 (FAS Completing Week 36)

A 8q8/3 group



B 8q8/5 group

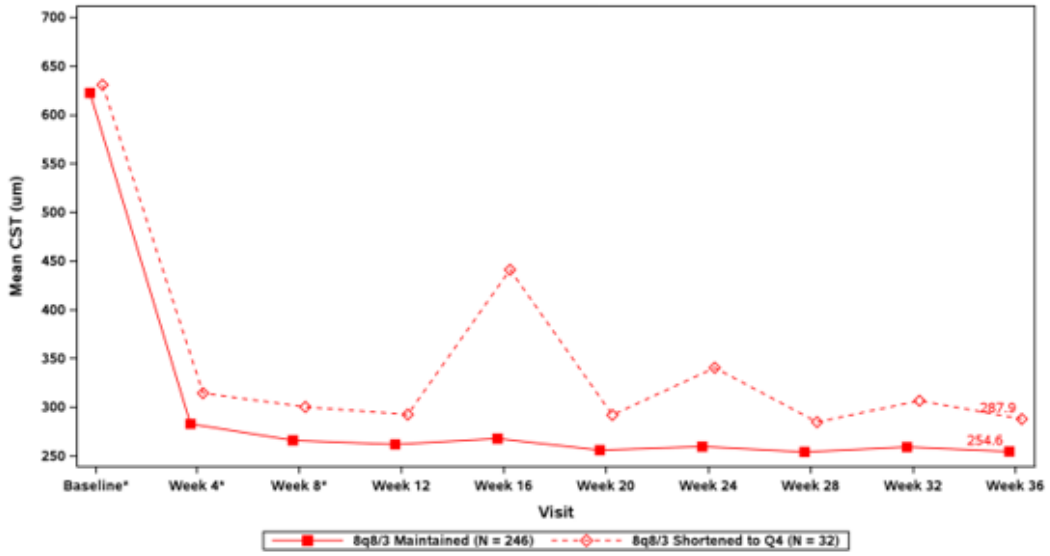


* Initial monthly doses.

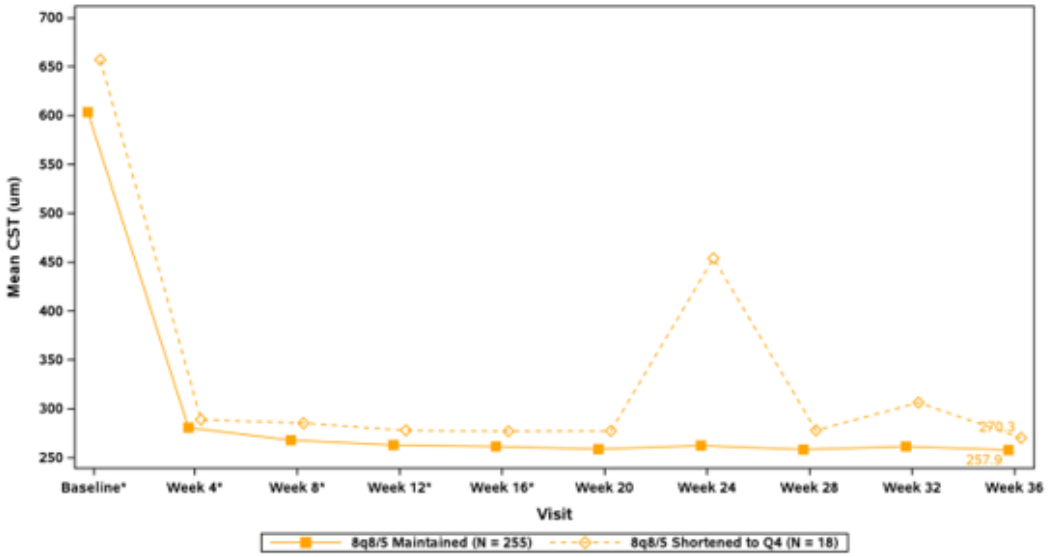
Figure 11: QUASAR: CST through Week 36 for participants on Q8 versus Q4 intervals

Mean CST (µm) by visit through Week 36 in the 8q8/3 (a) and 8q8/5 (b) groups in participants in the QUASAR study who maintained a Q8 Interval versus those whose Interval was shortened to Q4 (FAS Completing Week 36)

A 8q8/3 group



B 8q8/5 group



* Initial monthly doses.

- ***Provision of Week 64 efficacy***

Table 17: Change from baseline in BCVA measured by the ETDRS letter score at weeks 36, 44 and 64, MMRM (full analysis set)

		2q4 N = 301	8q8/3 N = 293	8q8/5 N = 298
W36	Baseline mean [a]	54.1	55.2	55.4
	Number of participants with Week 36 data (included/excluded due to ICE)	264/17	260/12	248/18
	Arithmetic mean (SD) change from baseline [a]	17.8 (13.1)	17.0 (11.8)	19.1 (11.2)
	LS mean (SE) change from baseline	17.5 (0.7)	17.4 (0.7)	18.3 (0.6)
	Contrast [b]		8q8/3 -2q4	8q8/5 -2q4
	Estimate for contrast and two-sided 95% CI [c]		-0.1 (-2.0, 1.9)	0.8 (-1.1, 2.7)
W44	Baseline mean [a]	54.1	-	55.4
	Number of participants with Week 44 data (included/excluded due to ICE)	266/10	-	247/11
	Arithmetic mean (SD) change from baseline [a]	18.0 (13.4)	-	19.7 (11.7)
	LS mean (SE) change from baseline	17.8 (0.7)		18.8 (0.7)
	Contrast [b]		-	8q8/5 -2q4
	Estimate for contrast and two-sided 95% CI [c]			1.0 (-1.0, 2.9)
W64	Baseline mean [a]	54.1	55.2	55.4
	Number of participants with Week 64 data (included/excluded due to ICE)	255/15	253/15	240/16
	Arithmetic mean (SD) change from baseline [a]	17.4 (14.6)	17.3 (12.7)	19.2 (13.0)
	LS mean (SE) change from baseline	17.3 (0.8)	17.8 (0.7)	18.1 (0.8)
	Contrast [b]		8q8/3 - 2q4	8q8/5 - 2q4
	Estimate for contrast and two-sided 95% CI [c]		0.5 (-1.6, 2.7)	0.7 (-1.5, 2.9)

APAC = Asia-Pacific; BCVA = best-corrected visual acuity; CI = Confidence Interval; ETDRS = early treatment diabetic retinopathy study; ICE = intercurrent event; LS = least squares; MMRM = mixed model for repeated measurements; RVO = retinal vein occlusion; SD = Standard Deviation; SE = Standard Error.

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

ICEs were handled according to primary estimand strategy as described in Table 4-2 in SAP Section 4.2.2.1 in W36 CSR Section 10.1.9.

(a) based on observed cases excluding data after ICE.

(b) The contrast also includes the interaction term for treatment x visit (at Weeks 36, 44 and 64, for details on the population-level summary see SAP Section 4.2.2 in W36 CSR Section 10.1.9).

(c) Estimate based on the MMRM, was computed for the differences of 8q8/3 minus 2q4 and 8q8/5 minus 2q4, respectively with two-sided 95% CIs.

See Definition of terms for treatment group description.

Table 18: Number of active injections from baseline to week 64, Main Analysis (full analysis set)

	2q4 (N=301)	8q8/3 (N=293)	8q8/5 (N=298)
Arithmetic mean (SD)	11.2	8.2	8.8
LS mean (SE) number of active injections	11.7 (0.1)	8.5 (0.1)	9.5 (0.1)
Contrast [a]		8q8/3 - 2q4	8q8/5 - 2q4
Estimate for contrast and two-sided 95% CI [a]		-3.2 (-3.5, -3.0)	-2.2 (-2.4, -2.0)
p-value [b]		<.0001	<.0001

APAC = Asia-Pacific; ANCOVA = Analysis of covariance; BCVA = best-corrected visual acuity; CI = Confidence Interval; CST = Central subfield thickness; ICE = intercurrent events; LS = least-square; SE Standard Error.

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

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

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

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

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

See Definition of terms for treatment group description.

Table 19: Proportion of participants gaining at least 15 letters in BCVA from baseline at week 64, OC excluding values after ICE (full analysis set)

	2q4 (N=301) Num/Den (%)	**8q8/3** (N=293) Num/Den (%)	**8q8/5** (N=298) Num/Den (%)
Participants who gained at least 15 letters	154/255 (60.4%)	156/253 (61.7%)	161/240 (67.1%)

ICE = intercurrent events; OC = observed cases

OC excluding values after ICE: observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 of the SAP Section 6.5 in W36 CSR Section 10.1.9.

Missing cases were not included in the denominator when calculating proportions.

See Definition of terms for treatment group description.

Table 20: Proportion of participants achieving ETDRS letter score of at least 69 at week 64, OC excluding values after ICE (full analysis set)

	2q4 (N=301) Num/Den (%)	**8q8/3** (N=293) Num/Den (%)	**8q8/5** (N=298) Num/Den (%)
Participants who achieved letter score of ≥ 69 letters	179/255 (70.2%)	178/253 (70.4%)	181/240 (75.4%)

ICE = intercurrent events; OC = observed cases

OC excluding values after ICE: observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 of the SAP Section 6.5 in W36 CSR Section 10.1.9.

Missing cases were not included in the denominator when calculating proportions.

See Definition of terms for treatment group description.

Table 21: Proportion of participants having no retinal fluid in the central subfield at week 64, OC excluding values after ICE (full analysis set)

	2q4 (N=301) Num/Den (%)	**8q8/3** (N=293) Num/Den (%)	**8q8/5** (N=298) Num/Den (%)
Participants with no IRF and no SRF	167/253 (66.0%)	193/253 (76.3%)	171/240 (71.3%)

ICE = intercurrent events; IRF = intraretinal fluid; OC = observed cases; SRF = subretinal fluid

OC excluding values after ICE : observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 of the SAP Section 6.5 in W36 CSR Section 10.1.9.

Missing cases were not included in the denominator when calculating proportions.

See Definition of terms for treatment group description.

Table 22: Change from baseline in CST (µm) at Week 64, MMRM (full analysis set)

	2q4 N = 301	8q8/3 N = 293	8q8/5 N = 298
Baseline mean [a]	651.0	626.1	609.2
Number of participants with Week 64 data (included/excluded due to ICE)	252/15	253/14	240/15
Arithmetic mean (SD) change from baseline [a]	-373.0 (252.1)	-355.5 (239.5)	-339.8 (229.6)
LS mean (SE) change from baseline	-353.7 (5.2)	-361.1 (4.3)	-353.3 (4.1)
Contrast [b]		8q8/3 - 2q4	8q8/5 - 2q4
Estimate for contrast and two- sided 95% CI [c]		-7.4 (-20.7, 5.9)	0.5 (-12.6, 13.5)

APAC = Asia-Pacific; BCVA = best-corrected visual acuity; CI = confidence interval; CST = central subfield retinal thickness; ICE = intercurrent events; LS = least squares; MMRM = mixed model for repeated measurements; RVO = retinal vein occlusion; SD = standard deviation; SE = standard error

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

ICEs were handled according to primary estimand strategy as described in Table 4-2 of the SAP Section 4.2.2.1 in W36 CSR Section 10.1.9.

(a) Based on observed cases excluding data after ICE

(b) The contrast also includes the interaction term for treatment x visit (at Week 64, for details on the population-level summary see SAP Section 4.2.2 in W36 CSR Section 10.1.9)

(c) Estimate based on the MMRM model, was computed for the differences of 8q8/3 minus 2q4 and 8q8/5 minus 2q4, respectively with two-sided 95% CIs.

See Definition of terms for treatment group description.

Table 23: Change from baseline in NEI-VFQ-25 total score at week 64, ANCOVA, LOCF (full analysis set)

Treatment	LS mean (SE) chg. from BL	Arith. mean (SD) chg. from BL (a)	Baseline mean (b)	Number of participants with week 64 data: included/excluded due to ICE	Contrast	DF	t-value	p-value (c)	Estimate for Contrast and two-sided 95% CI (d)
8q8/3 (N=293)	6.10 (0.66)	5.92 (12.47)	79.39	253/15	8q8/3 - 2q4	529	-1.24	0.2167	-1.11 (-2.9,0.65)
8q8/5 (N=298)	6.67 (0.63)	7.01 (12.42)	78.15	240/15	8q8/5 - 2q4	524	-0.62	0.5340	-0.54 (-2.3,1.17)
2q4 (N=301)	7.21 (0.60)	6.91 (12.47)	78.98	255/15					

BL = Baseline; CI = Confidence Interval; DF = Degrees of Freedom; ICE = Intercurrent Event; LS = Least Squares; SD = Standard Deviation; SE = Standard Error

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

Intercurrent events were handled according to sensitivity estimand strategy as described in Table 4-2 in section 4.2.2.1 of the SAP.

LOCF (last observation carried forward): last available observed value prior to ICE was used to impute missing data.

(a) Based on a mix of observed and imputed assessments.

(b) Based on observed assessments.

(c) p-value for the two-sided test.

(d) Estimate based on the ANCOVA model, was computed for the differences of 8q8/3 minus 2q4 and 8q8/5 minus 2q4, respectively with two-sided 95% CIs.

2q4: Aflibercept 2mg administered every 4 weeks.

8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.

8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 24: Proportion of participants with specific treatment intervals through week 64 (safety analysis set; only week 64 completers)

Number (%) of participants with the specified dosing		2q4 N = 270 (100%)	8q8/3 N = 269 (100%)	8q8/5 N = 256 (100%)	All 8 mg N = 525 (100%)
≥Q8 dosing interval from Week 32 through Week 64 [a]		189 (70.0%)			
≥Q8 dosing interval through Week 64 [b]			237 (88.1%)	233 (91.0%)	470 (89.5%)
Shortened to Q4 dosing interval anytime [c]		21 (7.8%)	32 (11.9%)	23 (9.0%)	55 (10.5%)
Extended dosing interval anytime [d]		252 (93.3%)	245 (91.1%)	232 (90.6%)	477 (90.9%)
Never extended dosing interval [e]		18 (6.7%)	24 (8.9%)	24 (9.4%)	48 (9.1%)
Last *intended* dosing interval [f]	Q4	21 (7.8%)	11 (4.1%)	10 (3.9%)	21 (4.0%)
	≥Q8	249 (92.2%)	258 (95.9%)	246 (96.1%)	504 (96.0%)
	≥Q12	210 (77.8%)	232 (86.2%)	219 (85.5%)	451 (85.9%)
	≥Q16	135 (50.0%)	173 (64.3%)	159 (62.1%)	332 (63.2%)
	Q20		109 (40.5%)		
Last *completed* dosing interval	Q4	35 (13.0%)	13 (4.8%)	9 (3.5%)	22 (4.2%)
	≥Q8	235 (87.0%)	256 (95.2%)	247 (96.5%)	503 (95.8%)
	≥Q12	183 (67.8%)	219 (81.4%)	201 (78.5%)	420 (80.0%)
	Q16		151 (56.1%)		

DRM = dose regimen modification; Q4 =every 4 weeks; Q8 = every 8 weeks; Q12 = every 12 weeks; Q16 = every 16 weeks; Q20 = every 20 weeks

Duration (weeks) = [(date of last study intervention prior to Week 36) - (date of first study intervention) +28]/7; 28 days were added because of the minimum 4-week dosing interval in the study. Only participants that did not discontinue study intervention prior to Week 64 are included (Week 64 completers).

(a) All participants on 2q4 extended to 8-week interval at the W32 visit for whom it was not planned to have their interval shortened to 4-week interval (according to DRM criteria until Week 60) prior to Week 64.

(b) All participants on 8q8 with 8-week or longer interval for whom it was not planned to have their interval shortened to 4-week interval (according to DRM criteria until Week 60) prior to Week 64.

(c) For 2q4 this includes participants that were extended to q8 dosing interval and subsequently shortened back to q4.

(d) All participants for whom it was planned to have their interval extended (according to DRM criteria until Week 60) prior to Week 64.

(e) All participants for whom it was not planned to have their interval extended (according to DRM criteria until Week 60) prior to Week 64.

(f) Based on DRM criteria assessed at the last visit with active injection before Week 64.

See Definition of terms for treatment group description.

The primary efficacy endpoint was the change from baseline in best-corrected visual acuity (BCVA), measured by the ETDRS letter score at Week 36.

According to the data provided by the Applicant, the primary objective is met at week 36 for QUASAR study, concerning 8q8/3 and 8q8/5 treatment.

- 8q8/3: Non-inferiority of Eylea 8q8/3 to Eylea 2q4 for the primary endpoint, BCVA change from baseline at week 36 in the study eye, is confirmed with a non-inferiority margin letters ($p<0.001$, assessed at a one-sided significance level of 0.025)

- 8q8/5: Non-inferiority of Eylea 8q8/5 to Eylea 2q4 for the primary endpoint, BCVA change from baseline at week 36 in the study eye, is confirmed with a non-inferiority margin letters ($p<0.001$, assessed at a one-sided significance level of 0.025).

Thus, the primary endpoint is achieved with results observed in the pooled RVO group in terms of BCVA improvements at Week 36.

A decrease in treatment efficacy was observed in terms of changes in BCVA from baseline, particularly at Week 16 for the 8q8/3 regimen and at Week 24 for the 8q8/5 regimen. This reduction in efficacy appeared to diverge from the data observed with the lower 2q4 dose; however, it was not considered clinically significant.

In this way, the Applicant highlighted that, in the 8q8/3 arm, patients had the opportunity at Weeks 16, 24, and 32 to increase the frequency of injections from Q8 to Q4 if they met protocol-specified

criteria for shortening the interval, based on loss of initial visual and anatomical improvements. In the 8q8/5 arm, patients had the same opportunity at Weeks 24 and 32.

This argument is fully supported and corresponds to the various observed time points, confirming the possibility of reducing the treatment interval. It is also noted and accepted that, as shown in Figures 10A and 10B, shortening the treatment interval in the QUASAR study allowed recovery of visual gain.

The Applicant was requested to provide the 64-week data from the QUASAR study, in order to draw conclusions on the long-term efficacy of the treatment and to further highlight the safety profile of the high doses used in this study. In this context, the Applicant has provided the requested 64-week data and analyses of the primary endpoint, key secondary endpoint, and secondary endpoints.

Primary efficacy endpoint:

Change from baseline in BCVA measured by the ETDRS letter score at Week 36 and Week 64

The primary efficacy endpoint was the change from baseline in best-corrected visual acuity (BCVA), measured using the ETDRS letter score at Week 36. According to the data provided by the Applicant, the primary objective of the QUASAR study was met at Week 36 for both 8q8/3 and 8q8/5 treatment groups. It is fully accepted that BCVA changes from baseline at Week 64 also met the pre-specified non-inferiority criteria for the Week 36 primary endpoint in both 8 mg groups compared with the 2 mg group.

Specifically, at Week 64, the LS mean changes from baseline in BCVA were 0.5 letters (95% CI: -1.6, 2.7) for 8q8/3 and 0.7 letters (95% CI: -1.5, 2.9) for 8q8/5, compared with 2q4. Non-inferiority was confirmed, as the lower bounds of the 95% confidence intervals exceeded -4 letters.

Key secondary efficacy endpoints:

Number of active injections from baseline to Week 64

The number of active injections from baseline was evaluated as a key secondary endpoint at Week 64.

According to the results provided by the Applicant, the 8q8/5 and 8q8/3 groups received a statistically significantly lower number of active injections (9.5 and 8.5, respectively) compared with the 2q4 group (11.7 active injections). The difference was particularly favourable for the 8q8/3 group, corresponding to 3 fewer injections over 64 weeks compared with 2q4. This corresponds to an 8 mg/3 dose being superior to 2 mg in terms of the key secondary endpoint.

The key secondary endpoint was thus achieved.

Secondary endpoint:

Change from baseline in BCVA measured by the ETDRS letter score at Week 44

The BCVA outcomes at Week 44 remained consistent with the results reported at Week 36.

The LS mean change from baseline in BCVA was comparable between the two groups, with 18.8 letters in the 8q8/5 group and 17.8 letters in the 2q4 group. At Week 44, the difference in LS mean changes from baseline between the groups was 1.0 letters (95% CI: -1.0, 2.9). Non-inferiority was demonstrated because the lower limit of the confidence interval was greater than -4, meeting the prespecified criteria. Thus, this secondary endpoint was achieved.

Change from baseline in BCVA measured by the ETDRS letter score at Week 64

see above in the assessment

Participant gaining at least 15 letters in BCVA from baseline at Weeks 36 and 64

According to the results provided by the Applicant, a slightly higher effect was observed in the 8q8/5 group; however, this difference is not considered clinically meaningful.

Indeed, in the Full Analysis Set (FAS), the proportions of participants who gained at least 15 letters in BCVA from baseline at Week 64—based on observed cases (OC) excluding values following intercurrent events (ICE)—were similar in the 2q4 and 8q8/3 groups (60.4% and 61.7%, respectively), while a slightly higher proportion was observed in the 8q8/5 group (67.1%). These results are consistent with those observed at Week 36.

Participant achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Weeks 36 and 64

At Week 64, the proportions of participants achieving an ETDRS score of at least 69 letters (approximately equivalent to 20/40 Snellen), based on observed cases excluding values after intercurrent events (ICE), were numerically higher in the 8q8/3 and 8q8/5 groups (70.4% and 75.4%, respectively) compared to the 2q4 group (70.2%). These results are consistent with those observed at Week 36.

Participant having no IRF and no SRF in the center subfield at Weeks 36 and 64

At Week 64, the proportion of participants with no retinal fluid in the central subfield appeared to vary between groups. From Week 36 onwards, a gradual decline in efficacy was observed over time; however, higher treatment doses appeared more effective than the lowest dose. The 8q8/3 and 8q8/5 groups (76.3% and 71.3%, respectively) showed higher proportions compared to the 2q4 group (66.0%), suggesting better disease control in the 8 mg groups.

Change from baseline in CST at Weeks 36 and 64

Based on the results provided by the Applicant, the least squares (LS) mean change from baseline decreases over time and is similar across all treatment groups. According to Table 22, "Change from baseline in CST at Week 64", the results support the non-inferiority of the 8q8/3 and 8q8/5 regimens compared to the 2q4 regimen. The estimated differences in LS mean changes in CST from baseline at Week 64 (95% CIs), based on the MMRM in the FAS, were small: -7.4 µm (95% CI: -20.7, 5.9) for 8q8/3 versus 2q4 and 0.5 µm (95% CI: -12.6, 13.5) for 8q8/5 versus 2q4. The different doses tested (8q8/3 and 8q8/5) did not show a significant advantage over the 2q4 dose in terms of CST change at Week 64. These results therefore suggest similar efficacy between the groups for this parameter.

Change from baseline in NEI-VFQ-25 total score at Weeks 36 and 64

At baseline, the mean NEI-VFQ-25 total scores were comparable across the three treatment groups, ranging from 78.15 to 79.39. Based on the MMRM analysis in the FAS, the estimated differences (95% CI) at Week 64 were: –1.11 points (95% CI: –2.9 to 0.65) for 8q8/3 vs. 2q4, and -0.54 points (95% CI: –2.3 to 1.17) for 8q8/5 vs. 2q4.

These results indicate no clinically meaningful differences between the groups. These results are consistent with those observed at Week 36.

Additional secondary endpoints:

Participant having last treatment interval ≥12 or of 16 weeks at Week 64, and Participant having next intended interval ≥12, ≥16 or of 20 weeks at Week 64.

Regarding the ≥Q8 interval, the difference between the last intended dosing interval (2q4: 92.2%; 8q8/3: 95.9%; 8q8/5: 96.1%) and the last completed dosing interval (2q4: 87.0%; 8q8/3: 95.2%; 8q8/5: 96.5%) is very small, particularly for the 8 mg treatment groups, where the values are almost identical.

Regarding the ≥Q4 interval, the difference between the last intended dosing interval (2q4: 7.8%; 8q8/3: 4.1%; 8q8/5: 3.5%) and the last completed dosing interval (2q4: 13.0%; 8q8/3: 4.8%; 8q8/5: 3.5%) shows some disparities. Notably, the 2q4 group demonstrates a larger gap, suggesting more frequent treatment adjustments than initially planned (last intended dosing interval 2q4: 7.8% vs last completed dosing interval 2q4: 13.0%). This also suggests a potential for reduced treatment burden when initiating treatment with 8 mg.

Regarding the ≥Q12 interval, the difference between the last intended dosing interval (2q4: 77.8%; 8q8/3: 86.2%; 8q8/5: 85.5%) and the last completed dosing interval (2q4: 67.8%; 8q8/3: 81.4%; 8q8/5: 78.5%) appears to be similar across groups. However, a larger difference is observed in the 2q4 group, suggesting that the intention to extend the interval was greater than what was achieved in practice.

With regard to the ≥Q16 dosing interval, the available data do not allow for definitive conclusions, as the results are incomplete across all treatment groups.

In view of all the data provided by the Applicant, it is agreed that the 8q8/3 treatment regimen demonstrates non-inferiority compared to the 2q4 regimen. From this perspective, the primary endpoint is met. Furthermore, it is also agreed that the key secondary endpoint is achieved, highlighting the superiority of the 8q8/3 regimen over 2q4.

In conclusion, non-inferiority has been observed between the 2q4 and 8q8/3 regimens.

Table 25: Change from baseline in BCVA measured by the ETDRS letter score at week 36, MMRM by RVO type (full analysis set)

RVO Type	BRVO			CRVO/HRVO		
	2q4 N = 149	8q8/3 N = 159	8q8/5 N = 159	2q4 N = 152	8q8/3 N = 134	8q8/5 N = 139
Baseline mean [a]	57.3	58.6	58.5	51.0	51.3	51.8
Number of participants with Week 36 data (included/excluded due to ICE)	131/8	140/5	134/11	133/9	120/7	114/7
Arithmetic mean (SD) change from baseline [a]	19.4 (11.0)	17.4 (10.9)	19.5 (10.0)	16.2 (14.7)	16.5 (12.7)	18.6 (12.6)
LS mean (SE) change from baseline	19.0 (0.8)	18.3 (0.8)	19.2 (0.7)	15.9 (1.2)	16.6 (1.1)	17.2 (1.2)
Contrast [b]		8q8/3 - 2q4	8q8/5 - 2q4		8q8/3 - 2q4	8q8/5 - 2q4
Estimate for contrast and two-sided 95% CI [c]		-0.8 (-2.9, 1.4)	0.2 (-1.9, 2.2)		0.6 (-2.6, 3.9)	1.3 (-2.0, 4.5)
Nominal p-value of one-sided test for non-inferiority at a margin of 4 letters		0.0018	<.0001		0.0027	0.0008

APAC = Asia-Pacific; BCVA = best-corrected visual acuity; CI = Confidence Interval; ETDRS = early treatment diabetic retinopathy study; ICE = intercurrent events; LS = least-squares; MMRM = mixed model for repeated measurements; RVO = retinal vein occlusion; SD = Standard Deviation; SE = Standard Error.

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

ICEs were handled according to primary estimand strategy as described in Table 4-2 of the SAP Section 4.2.2.1 in CRS Section 10.1.9.

(a) based on observed cases excluding data after ICE.

(b) The contrast also includes the interaction term for treatment x visit (at week 36, for details on the population-level summary see SAP Section 4.2.2 in CSR Section 10.1.9).

(c) Estimate based on the MMRM, was computed for the differences of 8q8/3 minus 2q4 and 8q8/5 minus 2q4, respectively with two-sided 95% CIs.

See Definition of terms for treatment group description.

In participants with BRVO, the least squares (LS) mean change from baseline in BCVA, as measured by the ETDRS letter score at Week 36, was 19.0 letters in the 2q4 group, 18.3 letters in the 8q8/3 group, and 19.2 letters in the 8q8/5 group.

For participants with CRVO/HRVO, the corresponding LS mean changes were 15.9, 16.6, and 17.2 letters, respectively.

The estimated differences (95% confidence intervals) in LS mean changes for BRVO participants were -0.8 letters (95% CI: -2.9 to 1.4) for 8q8/3 vs. 2q4, and 0.2 letters (95% CI: -1.9 to 2.2) for 8q8/5 vs 2q4.

In CRVO/HRVO participants, the differences were 0.6 letters (95% CI: -2.6 to 3.9) for 8q8/3 vs 2q4, and 1.3 letters (95% CI: -2.0 to 4.5) for 8q8/5 vs 2q4.

In both RVO subgroups, the results observed were consistent with those in the pooled RVO group, meeting the pre-defined criteria for non-inferiority in the overall population.

Table 26: Treatment group comparison: 8q8/5 vs 2q4

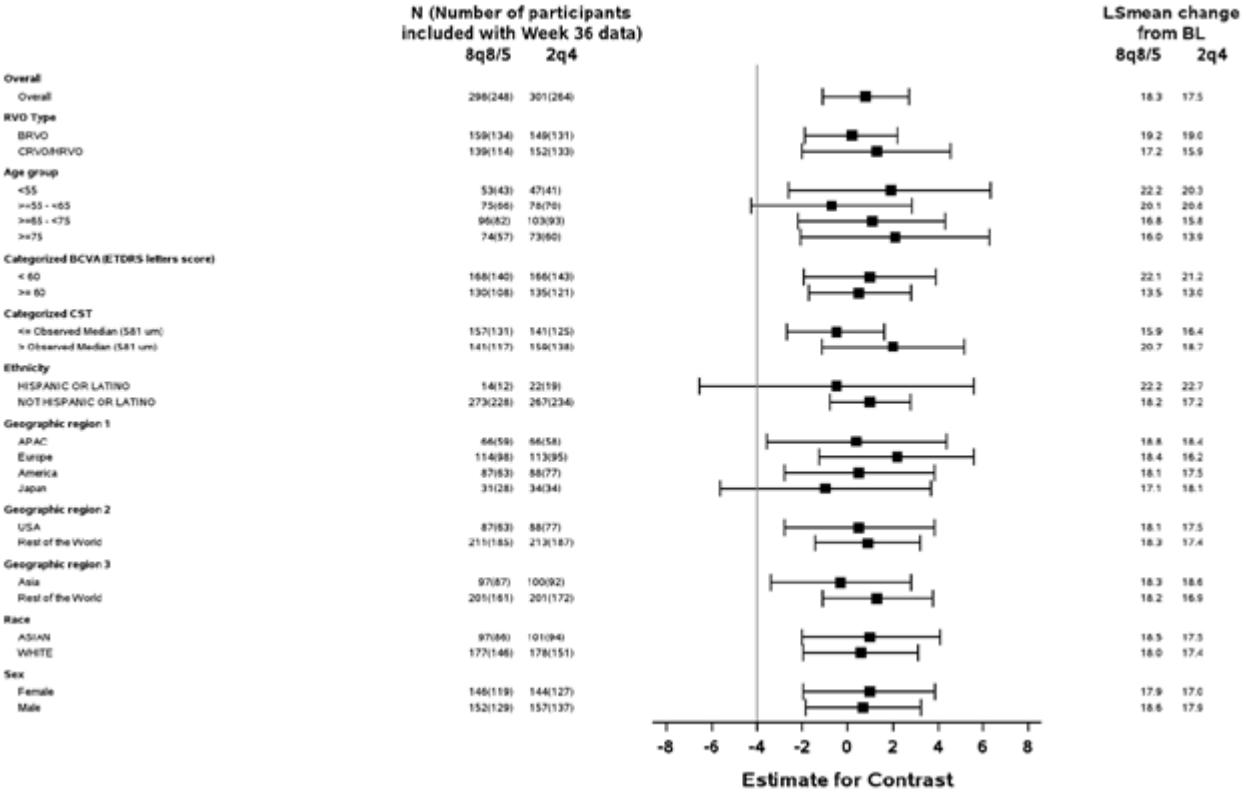
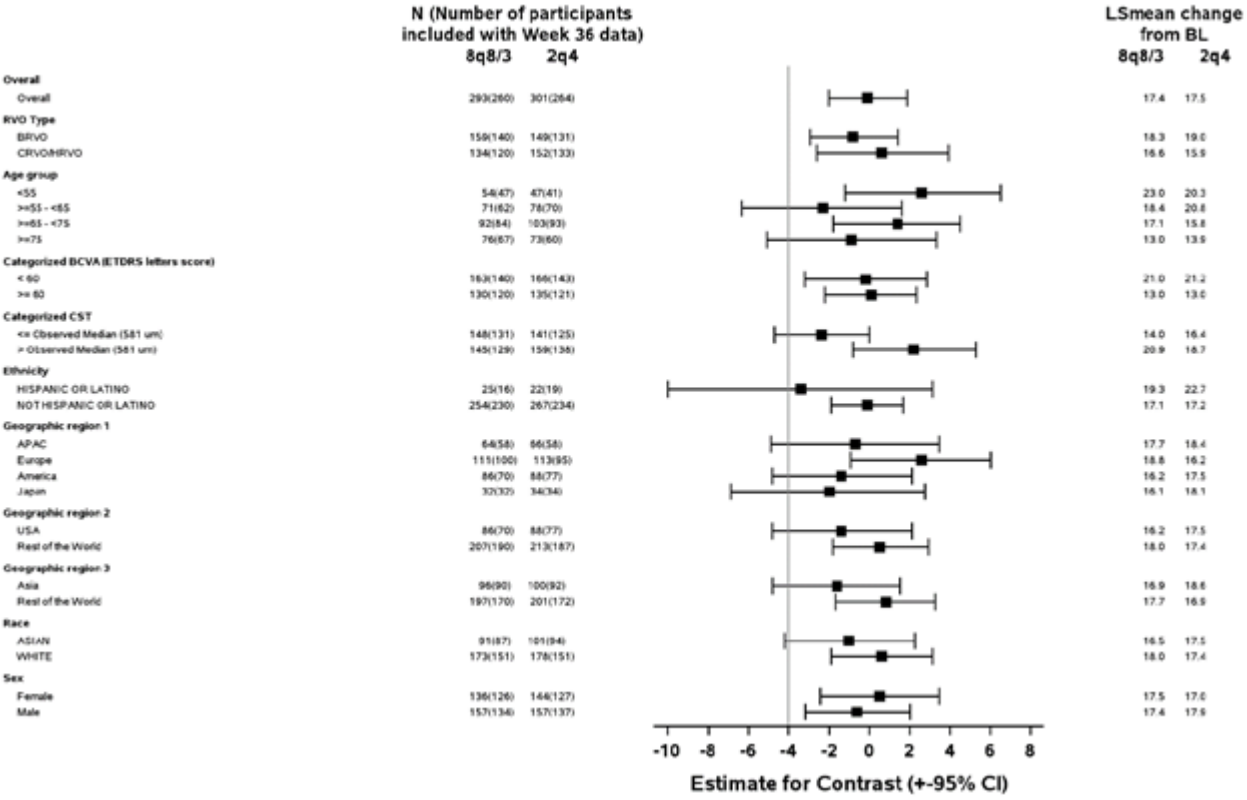


Table 27: Treatment group comparison: 8q8/3 vs 2q4



Subgroup analyses show results consistent with the overall result. Of note, the better homogeneity of subgroups for the 8 mg/5 arm for which almost all subgroups (88%=21/24) achieve the non-inferiority despite their smaller size.

– Secondary efficacy endpoint

○ *Number of active injections from baseline to week 36*

The number of active injections since baseline is a secondary endpoint for Week 36 and a key secondary endpoint for the upcoming Week 64 analysis.

Up to Week 36, the number of active injections was numerically lower in the 8q8/3 and 8q8/5 groups (6.1 and 6.9, respectively) compared to the 2q4 group, which received 8.8 active injections.

Table 28: Number of active injections from baseline to week 36, main analysis (full analysis set)

	2q4 (N=301)	8q8/3 (N=293)	8q8/5 (N=298)
LS mean (SE) number of active injections	8.8 (0.0)	6.1 (0.0)	6.9 (0.0)
Contrast [(a)]		8q8/3 - 2q4	8q8/5 - 2q4
Estimate for contrast and two-sided 95% CI [(a)]		-2.7 (-2.8, -2.6)	-1.8 (-1.9, -1.7)
p-value [(b)]		<.0001	<.0001

APAC = Asia-Pacific; ANCOVA = Analysis of covariance; BCVA = best-corrected visual acuity; CI = Confidence Interval; CST = Central subfield thickness; ICE = intercurrent events; LS = least-square; SE Standard Error.
Missing endpoint values were imputed using a multiple imputation approach as described in SAP Section 4.3.1.2 in CSR Section 10.1.9.
A non-parametric rank ANCOVA was used on each imputed data, adjusting for baseline BCVA, baseline CST, and the stratification variables (geographic region [Japan + APAC vs. Europe vs. America], BCVA score [<60 vs. ≥60], and RVO type [CRVO/HRVO vs. BRVO]) and results were combined using Rubin's rule.
ICEs were handled according to secondary estimand strategy as described in Table 4-6 of the SAP Section 4.3.1.3 in CSR Section 10.1.9.
(a) Based on the application of Rubin's rule after fitting a linear regression model adjusted for the same covariates as the non-parametric rank ANCOVA on each imputed dataset.
(b) Nominal p-value based on the non-parametric rank ANCOVA applied to each imputed dataset and combined using Rubin's rule.
See Definition of terms for treatment group description.
Source: Table 8.2.3/1

An arithmetic mean number of 8.5, 6.0 and 6.7 active injections for the 2q4, 8q8/3 and 8q8/5 groups, respectively, were administered from baseline to Week 36 based on OC (Table 8.2.3/3).

Results for analyses per RVO type are detailed in Section 5.1.5.2.1.

- ***Number of active injections from baseline to week 64***

Table 29: Number of active injections from baseline to week 64, main analysis (full analysis set)

	2q4 (N=301)	8q8/3 (N=293)	8q8/5 (N=298)
Arithmetic mean (SD)	11.2	8.2	8.8
LS mean (SE) number of active injections	11.7 (0.1)	8.5 (0.1)	9.5 (0.1)
Contrast [(a)]		8q8/3 - 2q4	8q8/5 - 2q4
Estimate for contrast and two-sided 95% CI [(a)]		-3.2 (-3.5, -3.0)	-2.2 (-2.4, -2.0)
p-value [(b)]		<.0001	<.0001

APAC = Asia-Pacific; ANCOVA = Analysis of covariance; BCVA = best-corrected visual acuity; CI = Confidence Interval; CST = Central subfield thickness; ICE = intercurrent events; LS = least-square; SE Standard Error.
Missing endpoint values were imputed using a multiple imputation approach as described in SAP Section 4.3.1.2 in W36 CSR Section 10.1.9.
A non-parametric rank ANCOVA was used on each imputed data, adjusting for baseline BCVA, baseline CST, and the stratification variables (geographic region [Japan + APAC vs. Europe vs. America], BCVA score [<60 vs. ≥60], and RVO type [CRVO/HRVO vs. BRVO]) and results were combined using Rubin's rule.
ICEs were handled according to secondary estimand strategy as described in Table 4-6 of the SAP Section 4.3.1.3 in W36 CSR Section 10.1.9.
(a) Based on the application of Rubin's rule after fitting a linear regression model adjusted for the same covariates as the non-parametric rank ANCOVA on each imputed dataset.
(b) p-value based on the non-parametric rank ANCOVA applied to each imputed dataset and combined using Rubin's rule.
See Definition of terms for treatment group description.

According to the results provided by the Applicant at week 36, the 8q8/3 and 8q8/5 groups received a numerically lower number of active injections (6.1 and 6.9, respectively) compared to the 2q4 group, which received 8.8 active injections. The same result is observed per RVO type (BRVO and CRVO/HRVO).

The number of active injections from baseline was evaluated as a key secondary endpoint at Week 64.

According to the results provided by the Applicant, the 8q8/5 and 8q8/3 groups received a statistically significantly lower number of active injections (9.5 and 8.5, respectively) compared with the 2q4 group (11.7 active injections). The difference was particularly favourable for the 8q8/3 group, corresponding to 3 fewer injections over 64 weeks compared with 2q4. This corresponds to an 8 mg/3 dose being superior to 2 mg in terms of the key secondary endpoint.

The key secondary endpoint was thus achieved.

- ***Gain of ≥15 letters from baseline at week 36 and at week 64***

In the FAS, the proportions of participants gaining at least 15 letters in BCVA from baseline at Week 36 using OC excluding values after ICE were similar in the 2q4 and 8q8/3 groups (59.8% and 58.8%, respectively) and slightly higher in the 8q8/5 treatment group (64.9%); the small numerical differences between the treatment groups were not clinically meaningful.

Table 30: Proportion of participants gaining at least 15 letters in BCVA from baseline at week 36, OC excluding values after ICE (full analysis set)

Visual and anatomic measures	2q4 N=301 Num/Den (%)	8q8/3 N=293 Num/Den (%)	8q8/5 N=298 Num/Den (%)
Participants who gained at least 15 letters	158/264 (59.8%)	153/260 (58.8%)	161/248 (64.9%)

ICE = intercurrent events; IRF = intraretinal fluid; OC = observed cases; SRF = subretinal fluid
OC excluding values after ICE : observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 of the SAP Section 6.5 in CSR Section 10.1.9.
Missing cases were not included in the denominator when calculating proportions.
See Definition of terms for treatment group description.

Table 31: Proportion of participants gaining at least 15 letters in BCVA from baseline at week 64, OC excluding values after ICE (full analysis set)

	2q4 (N=301) Num/Den (%)	8q8/3 (N=293) Num/Den (%)	8q8/5 (N=298) Num/Den (%)
Participants who gained at least 15 letters	154/255 (60.4%)	156/253 (61.7%)	161/240 (67.1%)

ICE = intercurrent events; OC = observed cases
OC excluding values after ICE: observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 of the SAP Section 6.5 in W36 CSR Section 10.1.9.
Missing cases were not included in the denominator when calculating proportions.
See Definition of terms for treatment group description.

According to the results provided by the Applicant, a slightly higher effect was observed in the 8q8/5 group; however, this difference is not considered clinically meaningful.

Indeed, in the Full Analysis Set (FAS), the proportions of participants who gained at least 15 letters in BCVA from baseline at Week 36—based on observed cases (OC) excluding values following intercurrent events (ICE)—were similar in the 2q4 and 8q8/3 groups (59.8% and 58.8%, respectively), while a slightly higher proportion was observed in the 8q8/5 group (64.9%).

The proportions of participants who gained at least 15 letters in BCVA from baseline at Week 64—based on observed cases (OC) excluding values following intercurrent events (ICE)—were similar in the 2q4 and 8q8/3 groups (60.4% and 61.7%, respectively), while a slightly higher proportion was observed in the 8q8/5 group (67.1%). These results are consistent with those observed at Week 36.

- ***EDTRS letter score of ≥69 at week 36 and at week 64***

Table 32: Proportion of participants achieving ETDRS letter score of at least 69 at week 36, OC excluding values after ICE (full analysis set)

Visual and anatomic measures	2q4 N=301 Num/Den (%)	8q8/3 N=293 Num/Den (%)	8q8/5 N=298 Num/Den (%)
Participants who achieved letter score of at least 69 letters	179/264 (67.8%)	189/260 (72.7%)	189/248 (76.2%)

ICE = intercurrent events; IRF = intraretinal fluid; OC = observed cases; SRF = subretinal fluid
OC excluding values after ICE : observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 of the SAP Section 6.5 in CSR Section 10.1.9.
Missing cases were not included in the denominator when calculating proportions.
See Definition of terms for treatment group description.

Table 33: Proportion of participants achieving ETDRS letter score of at least 69 at week 64, OC excluding values after ICE (full analysis set)

	2q4 (N=301) Num/Den (%)	8q8/3 (N=293) Num/Den (%)	8q8/5 (N=298) Num/Den (%)
Participants who achieved letter score of ≥ 69 letters	179/255 (70.2%)	178/253 (70.4%)	181/240 (75.4%)

ICE = intercurrent events; OC = observed cases

OC excluding values after ICE: observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 of the SAP Section 6.5 in W36 CSR Section 10.1.9.

Missing cases were not included in the denominator when calculating proportions.

See Definition of terms for treatment group description.

At Week 36, the proportions of participants achieving an ETDRS score of at least 69 letters (approximately equivalent to 20/40 Snellen), based on observed cases excluding values after intercurrent events (ICE), were numerically higher in the 8q8/3 and 8q8/5 groups (72.7% and 76.2%, respectively) compared to the 2q4 group (67.8%).

At Week 64, the proportions of participants achieving an ETDRS score of at least 69 letters (approximately equivalent to 20/40 Snellen), based on observed cases excluding values after intercurrent events (ICE), were numerically higher in the 8q8/3 and 8q8/5 groups (70.4% and 75.4%, respectively) compared to the 2q4 group (70.2%). These results are consistent with those observed at Week 36.

- ***No IRF and no SRF in central subfield at week 36 and at week 64***

The proportions of participants with no retinal fluid (no IRF and no SRF) in the central subfield at Week 36 using OC excluding values after ICE was high (>80%).

Table 34: Proportion of participants having no retinal fluid in the central subfield at week 36, OC excluding values after ICE (full analysis set)

Visual and anatomic measures	2q4 N=301 Num/Den (%)	8q8/3 N=293 Num/Den (%)	8q8/5 N=298 Num/Den (%)
Participants with no IRF and no SRF in central subfield	221/264 (83.7%)	211/260 (81.2%)	202/247 (81.8%)

ICE = intercurrent events; IRF = intraretinal fluid; OC = observed cases; SRF = subretinal fluid

OC excluding values after ICE : observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 of the SAP Section 6.5 in CSR Section 10.1.9.

Missing cases were not included in the denominator when calculating proportions.

See Definition of terms for treatment group description.

Table 35: Proportion of participants having no retinal fluid in the central subfield at week 64, OC excluding values after ICE (full analysis set)

	2q4 (N=301) Num/Den (%)	8q8/3 (N=293) Num/Den (%)	8q8/5 (N=298) Num/Den (%)
Participants with no IRF and no SRF	167/253 (66.0%)	193/253 (76.3%)	171/240 (71.3%)

ICE = intercurrent events; IRF = intraretinal fluid; OC = observed cases; SRF = subretinal fluid

OC excluding values after ICE : observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 of the SAP Section 6.5 in W36 CSR Section 10.1.9.

Missing cases were not included in the denominator when calculating proportions.

See Definition of terms for treatment group description.

Table 36: QUASAR: Retinal fluid status "dry" at week 36 by RVO type

OC excluding values after ICE (full analysis set)

RVO type	2q4 Num/Den (%)	8q8/3 Num/Den (%)	8q8/5 Num/Den (%)
Any	N=301	N=293	N=298
	221/264 (83.7%)	211/260 (81.2%)	202/247 (81.8%)
BRVO	N=149	N=159	N=159
	105/131 (80.2%)	114/140 (81.4%)	98/134 (73.1%)
CRVO/HRVO	N=152	N=134	N=139
	116/133 (87.2%)	97/120 (80.8%)	104/113 (92.0%)

At week 36, the proportion of participants with no retinal fluid in the central subfield is similar between groups. Specifically, 81.2% of participants in the 8q8/3 dosage group and 81.8% in the 8q8/5 dosage group showed absence of retinal fluid. A slightly higher efficacy was observed in the 2q4 dosage group, with 83.7% of participants having no retinal fluid; however, this difference is not clinically meaningful.

At Week 64, the proportion of participants with no retinal fluid in the central subfield appeared to vary between groups. From Week 36 onwards, a gradual decline in efficacy was observed over time; however, higher treatment doses appeared more effective than the lowest dose. The 8q8/3 and 8q8/5 groups (76.3% and 71.3%, respectively) showed higher proportions compared to the 2q4 group (66.0%), suggesting better disease control in the 8 mg groups.

One of the secondary objectives of the study was to assess the effect of aflibercept 8 mg Q8 compared with aflibercept 2 mg Q4 on additional visual and anatomical response measures. Accordingly, a secondary endpoint evaluated the proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the central subfield at Weeks 36 and 64.

As shown in Table 34, the overall proportion of participants with no retinal fluid in the central subfield ("dry" retinal status) at Week 36 was balanced across treatment groups, averaging 81% regardless of RVO type.

When analysed by RVO subtype and treatment at Week 36:

BRVO: 73.1% of participants in the 8q8/5 group achieved "dry" status, compared with higher proportions in the 2q4 (80.2%) and 8q8/3 (81.4%) groups.

CRVO/HRVO: 80.8% of participants in the 8q8/3 group achieved "dry" status, whereas higher proportions were observed in the 2q4 (87.2%) and 8q8/5 (92.0%) groups.

At Week 64, the overall proportion of participants with "dry" status remained higher in the aflibercept 8 mg groups (76.3% and 71.3% for 8q8/3 and 8q8/5, respectively) compared with the 2q4 group (66.0%).

When analysed by RVO subtype and treatment at Week 64:

BRVO: 61.9% (2q4) and 63.6% (8q8/5) of participants achieved "dry" status, compared with 77.9% in the 8q8/3 group.

CRVO/HRVO: 70.1% (2q4), 74.4% (8q8/3), and 80.2% (8q8/5) of participants achieved "dry" status.

Aflibercept 8 mg maintained higher rates of fluid-free status at Week 64 compared with 2 mg Q4. In BRVO, the 8q8/3 regimen showed the best outcomes, while in CRVO/HRVO, both 8 mg regimens—particularly 8q8/5—appear superior.

Given that the indication is not specific to the RVO subtypes, no further information will be requested.

- ***CST change from baseline at week 36 and at week 64***

Similar mean decreases from baseline in CST were observed in all treatment groups at Week 36.

Table 37: Change from baseline in CST (µm) at week 36, MMRM (full analysis set)

	2q4 N = 301	8q8/3 N = 293	8q8/5 N = 298
Baseline mean [a]	651.0	626.1	609.2
Number of participants with Week 36 data (included/excluded due to ICE)	262/17	260/11	247/18
Arithmetic mean (SD) change from baseline [a]	-397.3 (257.7)	-365.9 (239.9)	-351.0 (225.4)
LS mean (SE) change from baseline	-370.8 (3.9)	-370.9 (3.1)	-369.5 (2.3)
Contrast [b]		8q8/3 - 2q4	8q8/5 - 2q4
Estimate for contrast and two- sided 95% CI [c]		-0.1 (-10.0, 9.8)	1.2 (-7.7, 10.2)
P-value [d]		0.9804	0.7863

APAC = Asia-Pacific; BCVA = best-corrected visual acuity; CI = confidence interval; CST = central subfield retinal thickness; ICE = intercurrent events; LS = least squares; MMRM = mixed model for repeated measurements; RVO = retinal vein occlusion; SD = standard deviation; SE = standard error

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

ICEs were handled according to primary estimand strategy as described in Table 4-2 of the SAP Section 4.2.2.1 in CSR Section 10.1.9.

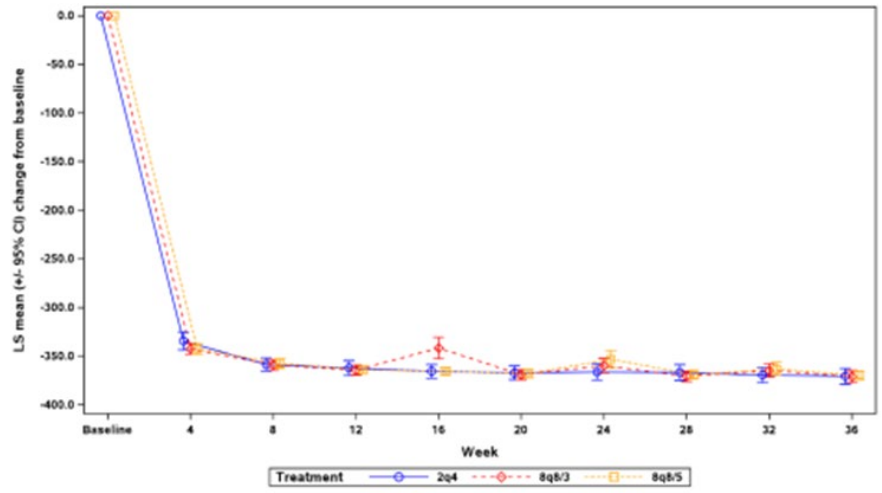
(a) Based on observed cases excluding data after ICE

(b) The contrast also includes the interaction term for treatment x visit (at week 36, for details on the population-level summary see SAP Section 4.2.2 in CSR Section 10.1.9)

(c) Estimate based on the MMRM model, was computed for the differences of 8q8/3 minus 2q4 and 8q8/5 minus 2q4, respectively with two-sided 95% CIs.

(d) p-value for the two-sided test.

See Definition of terms for treatment group description.



APAC = Asia-Pacific; CI = confidence interval; CST = central subfield retinal thickness; ICE = intercurrent events; LS = least squares; MMRM = mixed model for repeated measurements; RVO = retinal vein occlusion; SD = standard deviation; SE = standard error

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

ICEs were handled according to primary estimand strategy as described in Table 4-2 of the SAP Section 4.2.2.1 in CSR Section 10.1.9.

See Definition of terms for treatment group description.

Figure 12: Least-squares mean change from baseline in CST (um) by visit, MMRM (full analysis set)

Table 38: Change from baseline in CST (µm) at week 64, MMRM (full analysis set)

	2q4 N = 301	8q8/3 N = 293	8q8/5 N = 298
Baseline mean [(a)]	651.0	626.1	609.2
Number of participants with Week 64 data (included/excluded due to ICE)	252/15	253/14	240/15
Arithmetic mean (SD) change from baseline [(a)]	-373.0 (252.1)	-355.5 (239.5)	-339.8 (229.6)
LS mean (SE) change from baseline	-353.7 (5.2)	-361.1 (4.3)	-353.3 (4.1)
Contrast [(b)]		8q8/3 - 2q4	8q8/5 - 2q4
Estimate for contrast and two- sided 95% CI [(c)]		-7.4 (-20.7, 5.9)	0.5 (-12.6, 13.5)

APAC = Asia-Pacific; BCVA = best-corrected visual acuity; CI = confidence interval; CST = central subfield retinal thickness; ICE = intercurrent events; LS = least squares; MMRM = mixed model for repeated measurements; RVO = retinal vein occlusion; SD = standard deviation; SE = standard error

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

ICEs were handled according to primary estimand strategy as described in Table 4-2 of the SAP Section 4.2.2.1 in W36 CSR Section 10.1.9.

(a) Based on observed cases excluding data after ICE

(b) The contrast also includes the interaction term for treatment x visit (at Week 64, for details on the population-level summary see SAP Section 4.2.2 in W36 CSR Section 10.1.9)

(c) Estimate based on the MMRM model, was computed for the differences of 8q8/3 minus 2q4 and 8q8/5 minus 2q4, respectively with two-sided 95% CIs.

See Definition of terms for treatment group description.

Based on the results provided by the Applicant, the least squares (LS) mean change from baseline decreases over time and is similar across all treatment groups. According to Table 35, "Change from baseline in CST at Week 36", the p-value supports the non-inferiority of the 8q8/3 and 8q8/5 regimens compared to the 2q4 regimen.

Based on the results provided by the Applicant, the least squares (LS) mean change from baseline decreases over time and is similar across all treatment groups. According to Table 36, "Change from baseline in CST at Week 64", the results support the non-inferiority of the 8q8/3 and 8q8/5 regimens compared to the 2q4 regimen. The estimated differences in LS mean changes in CST from baseline at Week 64 (95% CIs), based on the MMRM in the FAS, were small: -7.4 µm (95% CI: -20.7, 5.9) for 8q8/3 versus 2q4 and 0.5 µm (95% CI: -12.6, 13.5) for 8q8/5 versus 2q4. The different doses tested (8q8/3 and 8q8/5) did not show a significant advantage over the 2q4 dose in terms of CST change at Week 64. These results therefore suggest similar efficacy between the groups for this parameter.

- **Change from baseline in NEI-VFQ-25 total score at week 36 and at week 64**

Mean increases from baseline were observed in all groups at Week 36 with generally minor numerical differences across treatment groups that were not considered clinically meaningful.

Table 39: Change from baseline in NEI-VFQ-25 total score at week 36, ANCOVA (full analysis set)

	2q4 N = 301	8q8/3 N = 293	8q8/5 N = 298
Baseline mean [a]	78.98	79.39	78.15
Number of participants with Week 36 data (included/excluded due to ICE)	263/17	259/12	249/17
Arithmetic mean (SD) change from baseline [b]	6.00 (13.03)	5.65 (11.37)	7.32 (12.50)
LS mean (SE) change from baseline	6.27 (0.67)	5.91 (0.61)	6.92 (0.63)
Contrast		8q8/3 - 2q4	8q8/5 - 2q4
Estimate for contrast and two- sided 95% CI [c]		-0.36 (-2.1, 1.40)	0.65 (-1.2, 2.45)
P-value [d]		0.6869	0.4792

ANCOVA = Analysis of covariance; APAC = Asia-Pacific; BCVA = best-corrected visual acuity; ICE = intercurrent events; CI = confidence interval; LS = least squares; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; RVO = retinal vein occlusion; SD = standard deviation, SE = standard error

An ANCOVA was used with baseline NEI-VFQ-25 total score measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs. ≥60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors.
Data after occurrence of an ICE was excluded in line with the sensitivity estimand strategy as described in Table 4-2 of the SAP section 4.2.2.1 in CSR Section 10.1.9.

(a) Based on observed assessments
(b) Based on observed assessment excluding data after ICEs.
(c) Estimate based on the ANCOVA model, was computed for the differences of 8q8/3 minus 2q4 and 8q8/5 minus 2q4, respectively with two-sided 95% CIs.
(d) p-value for the two-sided test.
See Definition of terms for treatment group description.

Table 40: Change from baseline in NEI-VFQ-25 total score at week 64, ANCOVA, LOCF (full analysis set)

Treatment	LS mean (SE) chg. from BL	Arith. mean (SD) chg. from BL (a)	Baseline mean (b)	Number of participants with week 64 data: included/excluded due to ICE	Contrast	DF	t-value	p-value (c)	Estimate for Contrast and two-sided 95% CI (d)
8q8/3 (N=293)	6.10 (0.66)	5.92 (12.47)	79.39	253/15	8q8/3 - 2q4	529	-1.24	0.2167	-1.11 (-2.9,0.65)
8q8/5 (N=298)	6.67 (0.63)	7.01 (12.42)	78.15	240/15	8q8/5 - 2q4	524	-0.62	0.5340	-0.54 (-2.3,1.17)
2q4 (N=301)	7.21 (0.60)	6.91 (12.47)	78.98	255/15					

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

At baseline, the mean NEI-VFQ-25 total scores were comparable across the three treatment groups, ranging from 78.15 to 79.39. Based on the MMRM analysis in the FAS, the estimated differences (95% CI) at Week X were: –0.36 points (95% CI: –2.10 to 1.40) for 8q8/3 vs. 2q4, and 0.65 points (95% CI: –1.20 to 2.45) for 8q8/5 vs. 2q4.

At baseline, the mean NEI-VFQ-25 total scores were comparable across the three treatment groups, ranging from 78.15 to 79.39. Based on the MMRM analysis in the FAS, the estimated differences (95% CI) at Week 64 were: –1.11 points (95% CI: –2.9 to 0.65) for 8q8/3 vs. 2q4, and -0.54 points (95% CI: –2.3 to 1.17) for 8q8/5 vs. 2q4.

These results indicate no clinically meaningful differences between the groups.

- ***Dosing only Q8W through week 36 and week 64 in the 8q8 group***

Table 41: Proportion of participants with specific treatment intervals through week 64 (safety analysis set; only week 64 completers)

Number (%) of participants with the specified dosing		2q4 N = 270 (100%)	8q8/3 N = 269 (100%)	8q8/5 N = 256 (100%)	All 8 mg N = 525 (100%)
≥Q8 dosing interval from Week 32 through Week 64 [a]		189 (70.0%)			
≥Q8 dosing interval through Week 64 [b]			237 (88.1%)	233 (91.0%)	470 (89.5%)
Shortened to Q4 dosing interval anytime [c]		21 (7.8%)	32 (11.9%)	23 (9.0%)	55 (10.5%)
Extended dosing interval anytime [d]		252 (93.3%)	245 (91.1%)	232 (90.6%)	477 (90.9%)
Never extended dosing interval [e]		18 (6.7%)	24 (8.9%)	24 (9.4%)	48 (9.1%)
Last *intended* dosing interval [f]	Q4	21 (7.8%)	11 (4.1%)	10 (3.9%)	21 (4.0%)
	≥Q8	249 (92.2%)	258 (95.9%)	246 (96.1%)	504 (96.0%)
	≥Q12	210 (77.8%)	232 (86.2%)	219 (85.5%)	451 (85.9%)
	≥Q16	135 (50.0%)	173 (64.3%)	159 (62.1%)	332 (63.2%)
	Q20		109 (40.5%)		
Last *completed* dosing interval	Q4	35 (13.0%)	13 (4.8%)	9 (3.5%)	22 (4.2%)
	≥Q8	235 (87.0%)	256 (95.2%)	247 (96.5%)	503 (95.8%)
	≥Q12	183 (67.8%)	219 (81.4%)	201 (78.5%)	420 (80.0%)
	Q16		151 (56.1%)		

DRM = dose regimen modification; Q4 =every 4 weeks; Q8 = every 8 weeks; Q12 = every 12 weeks; Q16 = every 16 weeks; Q20 = every 20 weeks

Duration (weeks) = [(date of last study intervention prior to Week 36) - (date of first study intervention) +28]/7; 28 days were added because of the minimum 4-week dosing interval in the study. Only participants that did not discontinue study intervention prior to Week 64 are included (Week 64 completers).

(a) All participants on 2q4 extended to 8-week interval at the W32 visit for whom it was not planned to have their interval shortened to 4-week interval (according to DRM criteria until Week 60) prior to Week 64.

(b) All participants on 8q8 with 8-week or longer interval for whom it was not planned to have their interval shortened to 4-week interval (according to DRM criteria until Week 60) prior to Week 64.

(c) For 2q4 this includes participants that were extended to q8 dosing interval and subsequently shortened back to q4.

(d) All participants for whom it was planned to have their interval extended (according to DRM criteria until Week 60) prior to Week 64.

(e) All participants for whom it was not planned to have their interval extended (according to DRM criteria until Week 60) prior to Week 64.

(f) Based on DRM criteria assessed at the last visit with active injection before Week 64.

See Definition of terms for treatment group description.

Table 42: Proportion of participants with specific treatment intervals through week 36 (safety analysis set; only participants considered as completers for Week 36)

	2q4 N = 287 (100%)	8q8/3 N = 278 (100%)	8q8/5 N = 273 (100%)	All 8 mg N = 551 (100%)
Participants with Q8 or longer dosing interval through Week 36 [a]		246 (88.5%)	255 (93.4%)	501 (90.9%)
Participants with Q4 as the last intended dosing interval [b]	70 (24.4%)	17 (6.1%)	18 (6.6%)	35 (6.4%)
Participants with Q8 as the last intended dosing interval [b]	217 (75.6%)	69 (24.8%)	255 (93.4%)	324 (58.8%)
Participants with Q12 as the last intended dosing interval [b]		192 (69.1%)		
Participants shortened to Q4 dosing interval anytime		32 (11.5%)	18 (6.6%)	50 (9.1%)
Participants shortening dosing interval at W16		17 (6.1%)		
Participants shortening dosing interval at W24		10 (3.6%)	13 (4.8%)	23 (4.2%)
Participants shortening dosing interval at W32		5 (1.8%)	5 (1.8%)	10 (1.8%)

DRM = dose regimen modification; Q4 =every 4 weeks; Q8 = every 8 weeks; Q12 = every 12 weeks

Duration (weeks) = [(date of last study intervention prior to Week 36) - (date of first study intervention) +28]/7; 28 days were added because of the minimum 4-week dosing interval in the study. Study interventions given at Week 36 or beyond are not included in this table.

Only participants that did not discontinue study intervention prior to Week 36 are included.

(a) All participants on Q8 interval for whom it was not planned to have their interval shortened (according to DRM criteria until Week 32) prior to Week 36.

(b) Based on DRM criteria assessed at the last visit with active injection before Week 36.

See Definition of terms for treatment group description.

Based on the results provided by the Applicant, the majority of participants maintained a Q8 or longer dosing interval through Week 36, with over 90% in both the 8q8/3 and 8q8/5 groups. Additionally, no significant differences in exposure to the study intervention were observed across the different types of RVO.

Participants having last treatment interval ≥12 or of 16 weeks at Week 64, and Participants having next intended interval ≥12, ≥16 or of 20 weeks at Week 64

Regarding the ≥Q8 interval, the difference between the last intended dosing interval (2q4: 92.2%; 8q8/3: 95.9%; 8q8/5: 96.1%) and the last completed dosing interval (2q4: 87.0%; 8q8/3: 95.2%; 8q8/5: 96.5%) is very small, particularly for the 8 mg treatment groups, where the values are almost identical.

Regarding the Q4 interval, the difference between the last intended dosing interval (2q4: 7.8%; 8q8/3: 4.1%; 8q8/5: 3.5%) and the last completed dosing interval (2q4: 13.0%; 8q8/3: 4.8%; 8q8/5: 3.5%) shows some disparities. This also suggests a potential for reduced treatment burden when initiating treatment with 8 mg.

Regarding the ≥Q12 interval, the difference between the last intended dosing interval (2q4: 77.8%; 8q8/3: 86.2%; 8q8/5: 85.5%) and the last completed dosing interval (2q4: 67.8%; 8q8/3: 81.4%; 8q8/5: 78.5%) appears to be similar across groups.

With regard to the ≥Q16 dosing interval, the available data do not allow for definitive conclusions, as the results are incomplete across all treatment groups.

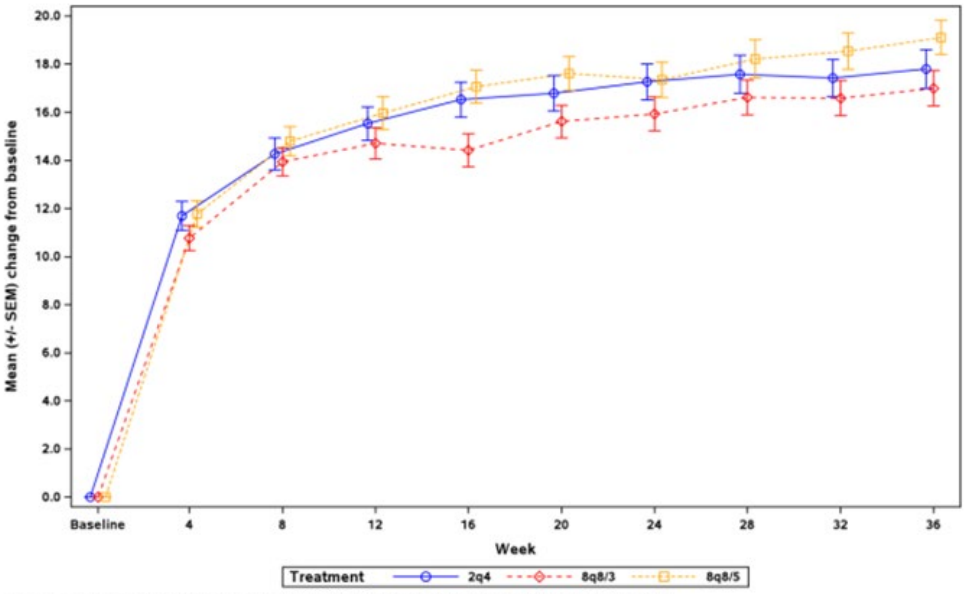
– Exploratory efficacy endpoints

○ *Change from baseline in BCVA measured by the ETDRS letter score at each visit*

Table 43: Summary statistics for BCVA measured by the ETDRS letter score by visit, OC excluding values after ICE (full analysis set)

		Value at Visit						Change from Baseline					
Treatment	Visit	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max
2q4 (N=301)	BASELINE	301	54.1 (14.3)	0.8	58.0	45.0, 65.0	24, 73						
	WEEK 4	297	65.7 (14.7)	0.9	69.0	58.0, 76.0	3, 93	297	11.7 (10.3)	0.6	11.0	6.0, 17.0	-35, 46
	WEEK 8	291	68.4 (14.8)	0.9	71.0	61.0, 79.0	16, 96	291	14.3 (11.3)	0.7	14.0	7.0, 20.0	-47, 53
	WEEK 12	289	69.4 (15.3)	0.9	74.0	63.0, 80.0	7, 94	289	15.5 (11.8)	0.7	15.0	9.0, 22.0	-52, 60
	WEEK 16	281	70.5 (15.5)	0.9	75.0	63.0, 81.0	9, 96	281	16.5 (12.2)	0.7	16.0	10.0, 23.0	-48, 57
	WEEK 20	276	70.9 (15.5)	0.9	75.0	64.0, 82.0	8, 99	276	16.8 (12.3)	0.7	16.0	10.0, 23.5	-55, 55
	WEEK 24	276	71.4 (15.8)	1.0	77.0	63.0, 82.0	7, 97	276	17.3 (12.4)	0.7	17.0	11.0, 23.0	-56, 54
	WEEK 28	268	71.8 (15.9)	1.0	76.0	64.5, 83.0	6, 96	268	17.6 (12.9)	0.8	17.0	11.0, 24.0	-57, 56
	WEEK 32	269	71.6 (15.9)	1.0	76.0	65.0, 82.0	7, 98	269	17.4 (12.6)	0.8	18.0	11.0, 24.0	-56, 56
	WEEK 36	264	72.0 (15.7)	1.0	76.0	65.0, 83.0	3, 96	264	17.8 (13.1)	0.8	17.0	11.0, 25.5	-60, 55
8q8/3 (N=293)	BASELINE	293	55.2 (13.6)	0.8	57.0	47.0, 67.0	24, 73						
	WEEK 4	291	66.2 (13.4)	0.8	69.0	60.0, 75.0	22, 93	291	10.8 (9.0)	0.5	10.0	4.0, 16.0	-17, 38
	WEEK 8	289	69.3 (14.2)	0.8	73.0	63.0, 79.0	6, 91	289	13.9 (9.9)	0.6	14.0	8.0, 20.0	-18, 40
	WEEK 12	283	70.1 (14.8)	0.9	74.0	61.0, 80.0	5, 95	283	14.7 (10.9)	0.7	14.0	9.0, 21.0	-19, 60
	WEEK 16	280	69.9 (15.4)	0.9	74.0	63.0, 80.0	0, 96	280	14.4 (11.4)	0.7	14.0	8.0, 21.0	-25, 44
	WEEK 20	278	71.1 (15.1)	0.9	75.0	64.0, 81.0	5, 95	278	15.6 (11.3)	0.7	15.0	9.0, 22.0	-19, 50
	WEEK 24	272	71.4 (15.1)	0.9	76.0	64.0, 81.0	4, 95	272	15.9 (11.5)	0.7	16.0	10.0, 21.5	-21, 45
	WEEK 28	268	72.1 (15.0)	0.9	76.0	65.0, 82.0	0, 97	268	16.6 (11.7)	0.7	16.0	10.0, 24.0	-24, 49
	WEEK 32	264	72.2 (14.6)	0.9	75.0	64.5, 83.0	5, 96	264	16.6 (11.8)	0.7	16.0	10.0, 23.0	-25, 50
	WEEK 36	260	72.8 (14.4)	0.9	76.0	67.5, 83.0	7, 96	260	17.0 (11.8)	0.7	16.5	10.0, 24.0	-22, 50
8q8/5 (N=298)	BASELINE	298	55.4 (13.4)	0.8	58.0	49.0, 66.0	18, 74						
	WEEK 4	293	67.3 (13.3)	0.8	70.0	61.0, 77.0	24, 91	293	11.8 (9.4)	0.6	11.0	6.0, 16.0	-27, 41
	WEEK 8	289	70.3 (13.0)	0.8	73.0	63.0, 80.0	22, 95	289	14.8 (10.2)	0.6	14.0	9.0, 21.0	-20, 47
	WEEK 12	285	71.6 (13.6)	0.8	75.0	65.0, 81.0	17, 93	285	16.0 (11.5)	0.7	16.0	10.0, 22.0	-37, 51
	WEEK 16	281	72.6 (13.5)	0.8	76.0	66.0, 83.0	22, 96	281	17.1 (11.6)	0.7	17.0	10.0, 24.0	-35, 53
	WEEK 20	271	73.4 (13.3)	0.8	77.0	67.0, 83.0	23, 98	271	17.6 (11.6)	0.7	17.0	11.0, 25.0	-31, 53
	WEEK 24	271	72.9 (14.2)	0.9	77.0	66.0, 82.0	18, 99	271	17.4 (12.1)	0.7	17.0	10.0, 25.0	-34, 57
	WEEK 28	265	73.9 (14.4)	0.9	78.0	68.0, 83.0	0, 100	265	18.2 (13.0)	0.8	18.0	11.0, 26.0	-60, 58
	WEEK 32	257	73.9 (13.8)	0.9	78.0	69.0, 83.0	15, 98	257	18.5 (12.1)	0.8	18.0	12.0, 26.0	-34, 53
	WEEK 36	248	74.6 (12.8)	0.8	78.0	69.0, 83.0	25, 99	248	19.1 (11.2)	0.7	18.0	12.0, 27.0	-14, 52

BCVA = Best corrected visual acuity; ETDRS = Early treatment diabetic retinopathy study; ICE = Intercurrent Event
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.



BCVA = Best corrected visual acuity; ETDRS = Early treatment diabetic retinopathy study; ICE = Intercurrent Event
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Bayer: /var/swan/root/bhc/865321/22153/stat/main01/prod/analysis/pgms/f_8_2_1_adeff_mean_cfb_bcva_oc_exice.sas 24JAN2025 15:02

Figure 13: Mean change from baseline in BCVA measured by the ETDRS letter score by visit, OC excluding values after ICE (full analysis set)

Table 44: Least-squares mean change from baseline in BCVA measured by the ETDRS letter score by visit, MMRM (full analysis set)

	2q4		8q8/3		8q8/5	
Visit	LS mean (SE) chg. from BL	95% CI for LS mean	LS mean (SE) chg. from BL	95% CI for LS mean	LS mean (SE) chg. from BL	95% CI for LS mean
WEEK 4	11.6 (0.6)	(10.5, 12.70)	10.8 (0.5)	(9.8, 11.80)	11.9 (0.5)	(10.9, 12.90)
WEEK 8	14.1 (0.6)	(12.8, 15.30)	14.1 (0.6)	(13.0, 15.20)	14.8 (0.5)	(13.7, 15.90)
WEEK 12	15.2 (0.6)	(13.9, 16.50)	15.0 (0.6)	(13.8, 16.20)	16.0 (0.6)	(14.8, 17.20)
WEEK 16	16.1 (0.7)	(14.8, 17.40)	14.7 (0.7)	(13.4, 16.00)	16.9 (0.6)	(15.7, 18.10)
WEEK 20	16.6 (0.7)	(15.2, 17.90)	16.0 (0.6)	(14.7, 17.30)	17.6 (0.6)	(16.4, 18.80)
WEEK 24	17.0 (0.7)	(15.7, 18.40)	16.3 (0.7)	(15.0, 17.60)	16.9 (0.7)	(15.5, 18.30)
WEEK 28	17.3 (0.7)	(15.9, 18.70)	16.9 (0.7)	(15.6, 18.30)	17.9 (0.7)	(16.4, 19.30)
WEEK 32	17.3 (0.7)	(15.9, 18.70)	17.0 (0.7)	(15.7, 18.40)	17.7 (0.7)	(16.3, 19.10)
WEEK 36	17.5 (0.7)	(16.1, 18.90)	17.4 (0.7)	(16.1, 18.80)	18.3 (0.6)	(17.0, 19.60)

BL Baseline; CI Confidence Interval; LS Least Squares.
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.>=60], and RVO type [CRVO/HRVO vs BRVO]) as fixed factors, and terms for the interaction between baseline BCVA and visit and treatment and visit. Covariance structure used: unstructured covariance structure.
Intercurrent events were handled according to primary estimand strategy as described in Table 4-2 in Section 4.2.2.1 of the SAP.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 45: Summary statistics for BCVA measured by the ETDRS letter score by RVO Type and visit, OC excluding values after ICE (full analysis set)

			Value at Visit						Change from Baseline					
RVO Type	Treatment	Visit	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max
BRVO	2q4 (N=149)	BASELINE	149	57.3 (13.2)	1.1	61.0	50.0, 68.0	24, 73						
		WEEK 4	147	69.4 (11.7)	1.0	72.0	62.0, 78.0	31, 89	147	12.0 (9.6)	0.8	11.0	6.0, 17.0	-13, 43
		WEEK 8	144	72.5 (11.4)	1.0	75.0	66.0, 80.0	36, 96	144	15.0 (10.7)	0.9	14.0	8.0, 20.0	-27, 50
		WEEK 12	140	73.9 (11.8)	1.0	77.0	69.0, 82.0	29, 94	140	16.8 (10.8)	0.9	15.0	10.0, 22.0	-7, 55
		WEEK 16	137	75.0 (11.5)	1.0	78.0	69.0, 83.0	34, 96	137	17.7 (11.1)	0.9	16.0	11.0, 22.0	-10, 57
		WEEK 20	137	75.2 (11.5)	1.0	78.0	70.0, 83.0	30, 99	137	18.1 (10.8)	0.9	16.0	11.0, 23.0	-4, 55
		WEEK 24	136	75.9 (11.5)	1.0	79.0	70.5, 83.0	33, 97	136	18.6 (10.7)	0.9	17.0	12.0, 23.0	-5, 54
		WEEK 28	131	76.3 (11.4)	1.0	79.0	72.0, 84.0	32, 96	131	19.1 (10.6)	0.9	17.0	12.0, 24.0	-3, 55
		WEEK 32	133	76.0 (11.5)	1.0	79.0	70.0, 84.0	33, 98	133	18.9 (10.1)	0.9	18.0	13.0, 22.0	-2, 55
		WEEK 36	131	76.6 (11.2)	1.0	80.0	70.0, 84.0	31, 96	131	19.4 (11.0)	1.0	17.0	12.0, 25.0	-5, 55
	8q8/3 (N=159)	BASELINE	159	58.6 (11.5)	0.9	60.0	53.0, 68.0	25, 73						
		WEEK 4	159	69.7 (10.9)	0.9	73.0	63.0, 78.0	32, 90	159	11.1 (9.2)	0.7	10.0	4.0, 17.0	-17, 38
		WEEK 8	158	73.1 (10.9)	0.9	76.0	69.0, 80.0	34, 91	158	14.5 (9.4)	0.7	14.0	9.0, 20.0	-6, 40
		WEEK 12	153	74.5 (11.2)	0.9	77.0	71.0, 82.0	31, 95	153	15.7 (10.7)	0.9	15.0	9.0, 21.0	-8, 60
		WEEK 16	151	73.9 (11.9)	1.0	76.0	69.0, 82.0	30, 95	151	15.1 (10.2)	0.8	14.0	8.0, 21.0	-14, 44
		WEEK 20	150	75.1 (11.3)	0.9	77.0	70.0, 83.0	29, 95	150	16.4 (9.5)	0.8	15.0	10.0, 22.0	-2, 44
		WEEK 24	149	75.6 (11.2)	0.9	78.0	71.0, 83.0	28, 95	149	16.8 (10.2)	0.8	17.0	11.0, 21.0	-18, 45
		WEEK 28	146	76.3 (10.5)	0.9	78.0	72.0, 84.0	33, 97	146	17.4 (10.3)	0.8	17.0	11.0, 23.0	-8, 49
		WEEK 32	144	75.8 (11.0)	0.9	78.0	71.0, 83.5	33, 96	144	16.8 (11.1)	0.9	16.0	10.5, 23.0	-16, 50
		WEEK 36	140	76.6 (10.8)	0.9	79.0	72.0, 84.0	26, 96	140	17.4 (10.9)	0.9	16.5	10.5, 24.0	-22, 50
	8q8/5 (N=159)	BASELINE	159	58.5 (11.5)	0.9	61.0	52.0, 68.0	28, 73						
		WEEK 4	156	69.9 (11.4)	0.9	72.0	63.0, 78.5	30, 89	156	11.2 (7.9)	0.6	10.0	6.0, 15.0	-7, 41
		WEEK 8	155	73.6 (10.8)	0.9	76.0	67.0, 81.0	30, 95	155	14.7 (9.1)	0.7	14.0	9.0, 20.0	-9, 47
		WEEK 12	152	75.0 (10.4)	0.8	77.0	69.0, 82.0	38, 93	152	16.0 (9.6)	0.8	15.5	10.0, 22.0	-8, 47
		WEEK 16	152	76.4 (10.3)	0.8	79.0	70.0, 84.0	42, 96	152	17.4 (9.7)	0.8	17.0	12.0, 23.0	-6, 53
		WEEK 20	144	76.9 (9.8)	0.8	79.0	71.0, 84.0	41, 98	144	17.9 (9.5)	0.8	16.5	12.0, 25.0	-3, 53
		WEEK 24	147	76.6 (11.5)	0.9	79.0	71.0, 84.0	18, 99	147	17.7 (10.9)	0.9	17.0	12.0, 24.0	-34, 57
		WEEK 28	145	76.9 (13.3)	1.1	80.0	73.0, 84.0	0, 100	145	18.1 (13.0)	1.1	18.0	12.0, 25.0	-60, 58
		WEEK 32	139	77.5 (11.2)	0.9	79.0	73.0, 85.0	18, 98	139	18.7 (11.3)	1.0	18.0	13.0, 25.0	-34, 53
		WEEK 36	134	78.1 (10.0)	0.9	80.0	74.0, 84.0	36, 99	134	19.5 (10.0)	0.9	18.0	13.0, 26.0	-4, 52

			Value at Visit						Change from Baseline					
RVO Type	Treatment	Visit	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max
CRVO/HRVO	2q4 (N=152)	BASELINE	152	51.0 (14.7)	1.2	54.0	40.0, 62.5	24, 73						
		WEEK 4	150	62.1 (16.4)	1.3	66.0	55.0, 74.0	3, 93	150	11.4 (11.0)	0.9	10.0	5.0, 17.0	-35, 46
		WEEK 8	147	64.4 (16.6)	1.4	68.0	56.0, 77.0	16, 93	147	13.6 (11.9)	1.0	13.0	6.0, 21.0	-47, 53
		WEEK 12	149	65.2 (17.1)	1.4	68.0	58.0, 79.0	7, 94	149	14.3 (12.5)	1.0	14.0	8.0, 22.0	-52, 60
		WEEK 16	144	66.2 (17.5)	1.5	70.0	58.0, 79.0	9, 95	144	15.4 (13.1)	1.1	15.5	8.0, 23.0	-48, 55
		WEEK 20	139	66.6 (17.6)	1.5	70.0	59.0, 79.0	8, 96	139	15.5 (13.5)	1.1	16.0	9.0, 24.0	-55, 44
		WEEK 24	140	67.0 (18.1)	1.5	71.0	59.5, 79.5	7, 97	140	15.9 (13.8)	1.2	17.0	8.0, 24.0	-56, 44
		WEEK 28	137	67.4 (18.3)	1.6	72.0	60.0, 81.0	6, 95	137	16.2 (14.6)	1.2	17.0	8.0, 24.0	-57, 56
		WEEK 32	136	67.2 (18.2)	1.6	72.0	60.5, 80.0	7, 97	136	16.0 (14.6)	1.2	16.5	7.5, 25.0	-56, 56
		WEEK 36	133	67.4 (18.1)	1.6	72.0	60.0, 80.0	3, 96	133	16.2 (14.7)	1.3	16.0	9.0, 26.0	-60, 50
	8q8/3 (N=134)	BASELINE	134	51.3 (14.8)	1.3	52.5	40.0, 63.0	24, 73						
		WEEK 4	132	62.0 (15.0)	1.3	65.0	53.5, 73.0	22, 93	132	10.4 (8.7)	0.8	9.0	3.5, 15.0	-10, 36
		WEEK 8	131	64.6 (16.3)	1.4	69.0	56.0, 77.0	6, 89	131	13.2 (10.5)	0.9	13.0	6.0, 20.0	-18, 40
		WEEK 12	130	65.0 (16.9)	1.5	69.0	55.0, 77.0	5, 92	130	13.5 (11.2)	1.0	14.0	8.0, 20.0	-19, 41
		WEEK 16	129	65.3 (17.7)	1.6	69.0	58.0, 79.0	0, 96	129	13.7 (12.6)	1.1	14.0	8.0, 21.0	-25, 41
		WEEK 20	128	66.4 (17.5)	1.5	70.0	58.5, 79.0	5, 95	128	14.8 (13.1)	1.2	14.0	8.0, 21.5	-19, 50
		WEEK 24	123	66.3 (17.4)	1.6	70.0	57.0, 79.0	4, 95	123	14.9 (12.9)	1.2	15.0	9.0, 22.0	-21, 45
		WEEK 28	122	67.0 (17.8)	1.6	69.5	59.0, 80.0	0, 95	122	15.7 (13.2)	1.2	16.0	10.0, 24.0	-24, 46
		WEEK 32	120	67.9 (17.1)	1.6	71.0	59.0, 81.0	5, 94	120	16.4 (12.6)	1.1	17.0	10.0, 23.0	-25, 48
		WEEK 36	120	68.3 (16.6)	1.5	71.0	59.5, 80.5	7, 93	120	16.5 (12.7)	1.2	16.5	9.5, 22.5	-21, 47

			Value at Visit						Change from Baseline					
RVO Type	Treatment	Visit	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max
	8q8/5 (N=139)	BASELINE	139	51.8 (14.5)	1.2	55.0	40.0, 63.0	18, 74						
		WEEK 4	137	64.4 (14.7)	1.3	68.0	57.0, 74.0	24, 91	137	12.4 (10.9)	0.9	12.0	6.0, 19.0	-27, 40
		WEEK 8	134	66.5 (14.3)	1.2	69.0	59.0, 77.0	22, 90	134	14.9 (11.4)	1.0	14.0	9.0, 21.0	-20, 42
		WEEK 12	133	67.7 (15.7)	1.4	71.0	61.0, 80.0	17, 92	133	15.9 (13.4)	1.2	16.0	9.0, 23.0	-37, 51
		WEEK 16	129	68.2 (15.3)	1.3	71.0	61.0, 80.0	22, 94	129	16.6 (13.5)	1.2	17.0	9.0, 24.0	-35, 53
		WEEK 20	127	69.3 (15.5)	1.4	72.0	61.0, 82.0	23, 94	127	17.3 (13.7)	1.2	18.0	10.0, 26.0	-31, 48
		WEEK 24	124	68.5 (15.9)	1.4	73.0	58.5, 80.0	20, 95	124	16.9 (13.3)	1.2	17.0	8.5, 26.0	-17, 53
		WEEK 28	120	70.2 (15.0)	1.4	73.5	60.5, 81.5	14, 95	120	18.4 (13.0)	1.2	18.0	10.0, 26.5	-16, 51
		WEEK 32	118	69.8 (15.4)	1.4	72.5	62.0, 80.0	15, 94	118	18.3 (13.0)	1.2	17.0	10.0, 28.0	-15, 48
		WEEK 36	114	70.6 (14.5)	1.4	74.0	63.0, 82.0	25, 95	114	18.6 (12.6)	1.2	17.5	11.0, 28.0	-14, 50

BCVA = Best corrected visual acuity; BRVO = Branch retinal vein occlusion; CRVO = Central retinal vein occlusion; ETDRS = Early treatment diabetic retinopathy study; HRVO = Hemiretinal vein occlusion; ICE = Intercurrent Event; RVO = Retinal vein occlusion
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

The mean change in BCVA tends to be similar between the treatment groups at the time points provided and showed an increase in BCVA up to week 36.

At baseline, the mean BCVA (±SD) was 54.1 (14.3) in 2q4 group, the mean BCVA (±SD) was 55.2 (13.6) and 55.4 (13.4) letters in 8q8/5 group. The mean (±SD) BCVA change from baseline to Week

16 was 16.1 (0.7) for 2q4 group, 14.7 (0.7) concerning the 8q8/3 group and 16.9 (0.6) for the 8q8/5 group, result observed in the OC excluding values after ICE (FAS).

According to the table 42, a decrease in efficacy is noted at Week 16 in the 8q8/3 group (mean change from baseline in BCVA: 14.7 [SE 0.7] at Week 16 vs. 15.0 [SE 0.6] at Week 12), and in the 8q8/5 group at both Week 24 (16.9 [SE 0.7] at Week 24 vs. 17.6 [SE 0.6] at Week 20) and Week 32 (17.7 [SE 0.7] at Week 32 vs. 17.9 [SE 0.7] at Week 28), based on the BCVA measured by the ETDRS letter score (FAS population).

According to Table 43, which presents BCVA (ETDRS letter score) by RVO subtype and visit, the decline in efficacy at Week 16 in the 8q8/3 group appears to occur only in the BRVO subgroup (mean: 73.9 [SD 11.9] at Week 16 vs. 74.5 [SD 11.2] at Week 12).

Similarly, the efficacy decrease observed at Weeks 24 and 32 in the 8q8/5 group corresponds to a decline in the BRVO subgroup at Week 24 (76.6 [SD 11.5] vs. 76.9 [SD 9.8] at Week 20), and in the CRVO/HRVO subgroup at Week 24 (68.5 [SD 15.9] vs. 69.3 [SD 15.5] at Week 20). At Week 32, the decline is only observed in the CRVO/HRVO subgroup (69.8 [SD 15.4] vs. 70.2 [SD 15.0] at Week 28).

- ***Proportion of participants with vision changes of at least 5, 10, or 15 letters in BCVA from baseline at each visit***

Table 46: Proportion of participants with vision changes of at least 5, 10 or 15 letters in BCVA from baseline at each visit, OC excluding values after ICE (full analysis set)

Visit		2q4 (N=301) Num/Den (%)	8q8/3 (N=293) Num/Den (%)	8q8/5 (N=298) Num/Den (%)
WEEK 4	Gained >= 15 letters	100/297 (33.7%)	91/291 (31.3%)	94/293 (32.1%)
	Gained >= 10 letters	171/297 (57.6%)	153/291 (52.6%)	168/293 (57.3%)
	Gained >= 5 letters	234/297 (78.8%)	214/291 (73.5%)	238/293 (81.2%)
	Gained > 0 letters	269/297 (90.6%)	260/291 (89.3%)	269/293 (91.8%)
	Lost >= 5 letters	8/297 (2.7%)	5/291 (1.7%)	5/293 (1.7%)
	Lost >= 10 letters	4/297 (1.3%)	3/291 (1.0%)	3/293 (1.0%)
	Lost >= 15 letters	2/297 (0.7%)	1/291 (0.3%)	3/293 (1.0%)
WEEK 8	Gained >= 15 letters	131/291 (45.0%)	135/289 (46.7%)	140/289 (48.4%)
	Gained >= 10 letters	196/291 (67.4%)	197/289 (68.2%)	206/289 (71.3%)
	Gained >= 5 letters	248/291 (85.2%)	238/289 (82.4%)	248/289 (85.8%)
	Gained > 0 letters	273/291 (93.8%)	268/289 (92.7%)	265/289 (91.7%)
	Lost >= 5 letters	5/291 (1.7%)	7/289 (2.4%)	5/289 (1.7%)
	Lost >= 10 letters	3/291 (1.0%)	2/289 (0.7%)	2/289 (0.7%)
	Lost >= 15 letters	3/291 (1.0%)	2/289 (0.7%)	1/289 (0.3%)
WEEK 12	Gained >= 15 letters	149/289 (51.6%)	138/283 (48.8%)	156/285 (54.7%)
	Gained >= 10 letters	210/289 (72.7%)	205/283 (72.4%)	216/285 (75.8%)
	Gained >= 5 letters	255/289 (88.2%)	238/283 (84.1%)	249/285 (87.4%)
	Gained > 0 letters	269/289 (93.1%)	264/283 (93.3%)	263/285 (92.3%)
	Lost >= 5 letters	9/289 (3.1%)	10/283 (3.5%)	8/285 (2.8%)
	Lost >= 10 letters	3/289 (1.0%)	5/283 (1.8%)	5/285 (1.8%)
	Lost >= 15 letters	3/289 (1.0%)	3/283 (1.1%)	4/285 (1.4%)
WEEK 16	Gained >= 15 letters	165/281 (58.7%)	136/280 (48.6%)	174/281 (61.9%)
	Gained >= 10 letters	216/281 (76.9%)	195/280 (69.6%)	217/281 (77.2%)
	Gained >= 5 letters	257/281 (91.5%)	242/280 (86.4%)	254/281 (90.4%)
	Gained > 0 letters	263/281 (93.6%)	258/280 (92.1%)	262/281 (93.2%)
	Lost >= 5 letters	9/281 (3.2%)	15/280 (5.4%)	8/281 (2.8%)
	Lost >= 10 letters	7/281 (2.5%)	9/280 (3.2%)	5/281 (1.8%)
	Lost >= 15 letters	6/281 (2.1%)	5/280 (1.8%)	3/281 (1.1%)
WEEK 20	Gained >= 15 letters	162/276 (58.7%)	142/278 (51.1%)	162/271 (59.8%)
	Gained >= 10 letters	213/276 (77.2%)	205/278 (73.7%)	214/271 (79.0%)
	Gained >= 5 letters	252/276 (91.3%)	245/278 (88.1%)	246/271 (90.8%)
	Gained > 0 letters	262/276 (94.9%)	261/278 (93.9%)	256/271 (94.5%)
	Lost >= 5 letters	7/276 (2.5%)	10/278 (3.6%)	7/271 (2.6%)
	Lost >= 10 letters	6/276 (2.2%)	8/278 (2.9%)	5/271 (1.8%)

Visit		2q4 (N=301) Num/Den (%)	8q8/3 (N=293) Num/Den (%)	8q8/5 (N=298) Num/Den (%)
	Lost >= 15 letters	4/276 (1.4%)	5/278 (1.8%)	3/271 (1.1%)
WEEK 24	Gained >= 15 letters	161/276 (58.3%)	150/272 (55.1%)	163/271 (60.1%)
	Gained >= 10 letters	217/276 (78.6%)	207/272 (76.1%)	206/271 (76.0%)
	Gained >= 5 letters	250/276 (90.6%)	243/272 (89.3%)	241/271 (88.9%)
	Gained > 0 letters	258/276 (93.5%)	253/272 (93.0%)	251/271 (92.6%)
	Lost >= 5 letters	9/276 (3.3%)	14/272 (5.1%)	13/271 (4.8%)
	Lost >= 10 letters	5/276 (1.8%)	8/272 (2.9%)	4/271 (1.5%)
	Lost >= 15 letters	4/276 (1.4%)	4/272 (1.5%)	2/271 (0.7%)
WEEK 28	Gained >= 15 letters	164/268 (61.2%)	153/268 (57.1%)	174/265 (65.7%)
	Gained >= 10 letters	208/268 (77.6%)	214/268 (79.9%)	217/265 (81.9%)
	Gained >= 5 letters	242/268 (90.3%)	242/268 (90.3%)	242/265 (91.3%)
	Gained > 0 letters	254/268 (94.8%)	249/268 (92.9%)	249/265 (94.0%)
	Lost >= 5 letters	8/268 (3.0%)	10/268 (3.7%)	10/265 (3.8%)
	Lost >= 10 letters	7/268 (2.6%)	8/268 (3.0%)	5/265 (1.9%)
	Lost >= 15 letters	4/268 (1.5%)	5/268 (1.9%)	3/265 (1.1%)
WEEK 32	Gained >= 15 letters	170/269 (63.2%)	151/264 (57.2%)	166/257 (64.6%)
	Gained >= 10 letters	212/269 (78.8%)	203/264 (76.9%)	211/257 (82.1%)
	Gained >= 5 letters	241/269 (89.6%)	232/264 (87.9%)	230/257 (89.5%)
	Gained > 0 letters	254/269 (94.4%)	247/264 (93.6%)	240/257 (93.4%)
	Lost >= 5 letters	9/269 (3.3%)	10/264 (3.8%)	5/257 (1.9%)
	Lost >= 10 letters	7/269 (2.6%)	4/264 (1.5%)	3/257 (1.2%)
	Lost >= 15 letters	4/269 (1.5%)	3/264 (1.1%)	2/257 (0.8%)
WEEK 36	Gained >= 15 letters	158/264 (59.8%)	153/260 (58.8%)	161/248 (64.9%)
	Gained >= 10 letters	210/264 (79.5%)	200/260 (76.9%)	207/248 (83.5%)
	Gained >= 5 letters	237/264 (89.8%)	231/260 (88.8%)	228/248 (91.9%)
	Gained > 0 letters	248/264 (93.9%)	245/260 (94.2%)	238/248 (96.0%)
	Lost >= 5 letters	9/264 (3.4%)	9/260 (3.5%)	5/248 (2.0%)
	Lost >= 10 letters	5/264 (1.9%)	4/260 (1.5%)	2/248 (0.8%)

Visit		2q4 (N=301) Num/Den (%)	8q8/3 (N=293) Num/Den (%)	8q8/5 (N=298) Num/Den (%)
	Lost >= 15 letters	4/264 (1.5%)	3/260 (1.2%)	0/248

BCVA = Best corrected visual acuity; ICE = Intercurrent Event
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
Missing cases will not be included in the denominator when calculating proportions.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 47: QUASAR: Categorized BCVA changes from baseline at week 36 by RVO type

OC excluding values after ICE (full analysis set)

			2q4 Num/Den (%)	8q8/3 Num/Den (%)	8q8/5 Num/Den (%)
BRVO			(N=149)	(N=159)	(N=159)
	Gain	≥ 15 letters	82/131 (62.6%)	82/140 (58.6%)	92/134 (68.7%)
		≥ 10 letters	112/131 (85.5%)	110/140 (78.6%)	121/134 (90.3%)
		≥ 5 letters	124/131 (94.7%)	129/140 (92.1%)	126/134 (94.0%)
		> 0 letters	128/131 (97.7%)	136/140 (97.1%)	131/134 (97.8%)
	Loss	≥ 5 letters	1/131 (0.8%)	1/140 (0.7%)	0/134
		≥ 10 letters	0/131	1/140 (0.7%)	0/134
		≥ 15 letters	0/131	1/140 (0.7%)	0/134
CRVO/HRVO			(N=152)	(N=134)	(N=139)
	Gain	≥ 15 letters	76/133 (57.1%)	71/120 (59.2%)	69/114 (60.5%)
		≥ 10 letters	98/133 (73.7%)	90/120 (75.0%)	86/114 (75.4%)
		≥ 5 letters	113/133 (85.0%)	102/120 (85.0%)	102/114 (89.5%)
		> 0 letters	120/133 (90.2%)	109/120 (90.8%)	107/114 (93.9%)
	Loss	≥ 5 letters	8/133 (6.0%)	8/120 (6.7%)	5/114 (4.4%)
		≥ 10 letters	5/133 (3.8%)	3/120 (2.5%)	2/114 (1.8%)
		≥ 15 letters	4/133 (3.0%)	2/120 (1.7%)	0/114

Table 48: Proportion of participants with vision changes of at least 5, 10 or 15 letters in BCVA from baseline at each visit, OC excluding values after ICE (full analysis set)

Visit		2q4 (N=301) Num/Den (%)	8q8/3 (N=293) Num/Den (%)	8q8/5 (N=298) Num/Den (%)
	Gained >= 5 letters	227/254 (89.4%)	219/254 (86.2%)	218/239 (91.2%)
	Gained > 0 letters	235/254 (92.5%)	228/254 (89.8%)	228/239 (95.4%)
	Lost >= 5 letters	11/254 (4.3%)	14/254 (5.5%)	8/239 (3.3%)
	Lost >= 10 letters	8/254 (3.1%)	8/254 (3.1%)	5/239 (2.1%)
	Lost >= 15 letters	5/254 (2.0%)	5/254 (2.0%)	4/239 (1.7%)
WEEK 64	Gained >= 15 letters	154/255 (60.4%)	156/253 (61.7%)	161/240 (67.1%)
	Gained >= 10 letters	187/255 (73.3%)	200/253 (79.1%)	193/240 (80.4%)
	Gained >= 5 letters	221/255 (86.7%)	224/253 (88.5%)	216/240 (90.0%)
	Gained > 0 letters	233/255 (91.4%)	230/253 (90.9%)	227/240 (94.6%)
	Lost >= 5 letters	12/255 (4.7%)	13/253 (5.1%)	10/240 (4.2%)
	Lost >= 10 letters	7/255 (2.7%)	6/253 (2.4%)	5/240 (2.1%)
	Lost >= 15 letters	6/255 (2.4%)	3/253 (1.2%)	3/240 (1.3%)

BCVA = Best corrected visual acuity; ICE = Intercurrent Event
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
Missing cases will not be included in the denominator when calculating proportions.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 49: Proportion of participants with vision changes of at least 5, 10 or 15 letters in BCVA from baseline at each visit by RVO Type, OC excluding values after ICE (full analysis set)

RVO Type: BRVO

Visit		2q4 (N=149) Num/Den (%)	8q8/3 (N=159) Num/Den (%)	8q8/5 (N=159) Num/Den (%)
WEEK 60	Gained >= 15 letters	78/125 (62.4%)	81/137 (59.1%)	93/128 (72.7%)
	Gained >= 10 letters	109/125 (87.2%)	107/137 (78.1%)	111/128 (86.7%)
	Gained >= 5 letters	120/125 (96.0%)	121/137 (88.3%)	123/128 (96.1%)
	Gained > 0 letters	124/125 (99.2%)	127/137 (92.7%)	125/128 (97.7%)
	Lost >= 5 letters	0/125	2/137 (1.5%)	2/128 (1.6%)
	Lost >= 10 letters	0/125	2/137 (1.5%)	0/128
	Lost >= 15 letters	0/125	1/137 (0.7%)	0/128
WEEK 64	Gained >= 15 letters	82/126 (65.1%)	87/136 (64.0%)	87/129 (67.4%)
	Gained >= 10 letters	106/126 (84.1%)	112/136 (82.4%)	108/129 (83.7%)
	Gained >= 5 letters	121/126 (96.0%)	124/136 (91.2%)	119/129 (92.2%)
	Gained > 0 letters	124/126 (98.4%)	129/136 (94.9%)	124/129 (96.1%)
	Lost >= 5 letters	0/126	3/136 (2.2%)	3/129 (2.3%)
	Lost >= 10 letters	0/126	2/136 (1.5%)	1/129 (0.8%)
	Lost >= 15 letters	0/126	1/136 (0.7%)	1/129 (0.8%)

BCVA = Best corrected visual acuity; ICE = Intercurrent Event; RVO = Retinal vein occlusion
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
Missing cases will not be included in the denominator when calculating proportions.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 50: Proportion of participants with vision changes of at least 5, 10 or 15 letters in BCVA from baseline at each visit by RVO Type, OC excluding values after ICE (full analysis set) (cont.)

RVO Type: CRVO/HRVO

Visit		2q4 (N=152) Num/Den (%)	8q8/3 (N=134) Num/Den (%)	8q8/5 (N=139) Num/Den (%)
WEEK 60	Gained >= 15 letters	73/129 (56.6%)	72/117 (61.5%)	72/111 (64.9%)
	Gained >= 10 letters	89/129 (69.0%)	88/117 (75.2%)	88/111 (79.3%)
	Gained >= 5 letters	107/129 (82.9%)	98/117 (83.8%)	95/111 (85.6%)
	Gained > 0 letters	111/129 (86.0%)	101/117 (86.3%)	103/111 (92.8%)
	Lost >= 5 letters	11/129 (8.5%)	12/117 (10.3%)	6/111 (5.4%)
	Lost >= 10 letters	8/129 (6.2%)	6/117 (5.1%)	5/111 (4.5%)
	Lost >= 15 letters	5/129 (3.9%)	4/117 (3.4%)	4/111 (3.6%)
WEEK 64	Gained >= 15 letters	72/129 (55.8%)	69/117 (59.0%)	74/111 (66.7%)
	Gained >= 10 letters	81/129 (62.8%)	88/117 (75.2%)	85/111 (76.6%)
	Gained >= 5 letters	100/129 (77.5%)	100/117 (85.5%)	97/111 (87.4%)
	Gained > 0 letters	109/129 (84.5%)	101/117 (86.3%)	103/111 (92.8%)
	Lost >= 5 letters	12/129 (9.3%)	10/117 (8.5%)	7/111 (6.3%)
	Lost >= 10 letters	7/129 (5.4%)	4/117 (3.4%)	4/111 (3.6%)
	Lost >= 15 letters	6/129 (4.7%)	2/117 (1.7%)	2/111 (1.8%)

BCVA = Best corrected visual acuity; ICE = Intercurrent Event; RVO = Retinal vein occlusion
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
Missing cases will not be included in the denominator when calculating proportions.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Across all treatment groups, a numerical difference was observed, with treatment 8q8/5 arm showing higher efficacy compared to 2q4 and 8q8/3 arms— particularly from Week 8 onward and with respect to the proportions of patients gaining ≥10 and ≥15 letters. However, these differences do not appear to be clinically meaningful.

A numerical difference was observed, with the 8q8/5 treatment showing higher efficacy compared to 2q4 and 8q8/3; however, these differences do not appear to be clinically meaningful. The Applicant was advised to provide a table including subgroup analyses by RVO subtype.

Concerning the week 36 for any RVO (Table 45)

Regarding the analysis of this table, the results provided by the Applicant did not show any numerical differences at Week 36, although for BRVO, the percentages of patients gaining ≥10 and ≥15 letters were numerically higher in the 8q8/5 group compared with 2q4 and 8q8/3.

Concerning the week 64 for any RVO (QUASAR W64 Table 46):

Based on the 64-week data, the proportion of participants with BCVA changes of at least 5, 10, or 15 letters from baseline at each visit, for any RVO type, appeared well balanced across treatment groups. No significant differences were observed.

Concerning the week 64 by RVO subgroup (QUASAR W64 Post-hoc analysis by RVO type Table 47, Table 48):

Focusing on the RVO subgroups (BRVO or CRVO/HRVO), some nuances are observed. For BRVO, the proportions are well balanced across treatments. In the CRVO/HRVO subgroup, differences are noted, although they do not appear to be statistically or clinically significant. Efficacy appears higher with the 8q8/5 treatment compared to 2q4 and 8q8/3 for patients gaining ≥15 letters (66.7% for 8q8/5, 59.0% for 8q8/3, and 55.8% for 2q4), and this non-clinically significant trend is also observed for gains ≥10 and ≥5 letters.

The data provided by the Applicant are acceptable and endorsed.

- ***Participant with no IRF and no SRF in the central subfield at each visit***

Table 51: QUASAR: Time to event analyses for retinal fluid status over week 36 by RVO type

Kaplan-Meier-estimated time-to-event analyses, using the specified parameters. Full analysis set

		BRVO			CRVO/HRVO		
		2q4 (N=149)	8q8/3 (N=159)	8q8/5 (N=159)	2q4 (N=152)	8q8/3 (N=134)	8q8/5 (N=139)
Fluid-free retina	No. of events	129	138	134	141	118	129
	No. of censored participants	19	21	25	10	16	10
	Median (95% CI) (weeks)	4.0 (NE, NE)	4.0 (4.0, 8.0)	8.0 (4.0, 8.0)	4.0 (4.0, 8.0)	4.0 (4.0, 8.0)	4.0 (NE, NE)
	Q1, Q3 (weeks)	4.0, 8.0	4.0, 12.0	4.0, 12.0	4.0, 8.0	4.0, 12.0	4.0, 8.0
	Estimated event rate at Week 36	0.9025	0.8794	0.8647	0.9449	0.8937	0.9464
	Hazard ratio [a]		0.9173	0.8563		0.8561	1.0395
	p-value [b]		0.3598	0.0867		0.0867	0.7094
IRF-free retina	No. of events	127	140	131	141	116	130
	No. of censored participants	18	18	23	9	15	7
	Median (95% CI) (weeks)	4.0 (NE, NE)	4.0 (NE, NE)	4.0 (NE, NE)	4.0 (NE, NE)	4.0 (NE, NE)	4.0 (NE, NE)
	Q1, Q3 (weeks)	4.0, 8.0	4.0, 8.0	4.0, 12.0	4.0, 8.0	4.0, 8.0	4.0, 4.0
	Estimated event rate at Week 36	0.9017	0.8921	0.8720	0.9509	0.8968	0.9618
	Hazard ratio [a]		0.9611	0.9007		0.8957	1.0627
	p-value [b]		0.6467	0.2008		0.1573	0.4318
SRF-free retina	No. of events	79	103	101	103	105	99
	No. of censored participants	2	1	0	0	0	2
	Median (95% CI) (weeks)	4.0 (NE, NE)	4.0 (NE, NE)	4.0 (NE, NE)	4.0 (NE, NE)	4.0 (NE, NE)	4.0 (NE, NE)
	Q1, Q3 (weeks)	4.0, 4.0	4.0, 8.0	4.0, 8.0	4.0, 8.0	4.0, 8.0	4.0, 4.0
	Estimated event rate at Week 36	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
	Hazard ratio [a]		0.9256	0.8997		0.9536	1.0905
	p-value [b]		0.3517	0.1757		0.5464	0.3080

BCVA = Best corrected visual acuity; NE = Not evaluable; RVO = Retinal vein occlusion; SRF = Subretinal fluid

Time to SRF-free retina is defined as the time from randomization to the time where a participant did not have any SRF in the central subfield for the first time as found in the SD-OCT (regardless of whether any retinal fluid was found again after that). Time to SRF-free retina was analysed using the Kaplan-Meier method, using the study visits (i.e. multiples of 4 weeks) and not the calendar time as unit. Intercurrent events (ICE) were handled according to primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.

(a) Hazard ratio was calculated using a stratified Cox proportional hazards model comparing 8mg groups vs. 2mg, including geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.>=60], and RVO type [CRVO/HRVO vs BRVO] as strata.

(b) p-value was calculated using a stratified log-rank test comparing 8mg groups vs. 2mg, including geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.>=60], and RVO type [CRVO/HRVO vs BRVO]) as strata.

Table 52: Proportion of participants with no IRF and no SRF in the central subfield at each visit, OC excluding values after ICE (full analysis set)

Visit	Fluid status	2q4 (N=301) Num/Den (%)	8q8/3 (N=293) Num/Den (%)	8q8/5 (N=298) Num/Den (%)
BASELINE	Dry	1/301 (0.3%)	0/293	0/298
	Not Dry	300/301 (99.7%)	293/293 (100.0%)	298/298 (100.0%)
	IRF and SRF	180/301 (60.0%)	205/293 (70.0%)	195/298 (65.4%)
	IRF only	116/301 (38.7%)	84/293 (28.7%)	96/298 (32.2%)
	SRF only	4/301 (1.3%)	4/293 (1.4%)	7/298 (2.3%)
	Missing or undefined	0	0	0
WEEK 4	Dry	173/294 (58.8%)	149/291 (51.2%)	169/291 (58.1%)
	Not Dry	121/294 (41.2%)	142/291 (48.8%)	122/291 (41.9%)
	IRF and SRF	13/294 (10.7%)	20/291 (14.1%)	14/291 (11.5%)
	IRF only	73/294 (60.3%)	70/291 (49.3%)	69/291 (56.6%)
	SRF only	35/294 (28.9%)	52/291 (36.6%)	39/291 (32.0%)
	Missing or undefined	1	0	1
	Both missing or undetermined	0	0	0
	IRF missing or undetermined (and SRF=No)	0	0	1
	SRF missing or undetermined (and IRF=No)	1	0	0
WEEK 8	Dry	223/291 (76.6%)	199/289 (68.9%)	209/289 (72.3%)
	Not Dry	68/291 (23.4%)	90/289 (31.1%)	80/289 (27.7%)
	IRF and SRF	5/291 (7.4%)	7/289 (7.8%)	9/289 (11.3%)
	IRF only	58/291 (85.3%)	72/289 (80.0%)	64/289 (80.0%)
	SRF only	5/291 (7.4%)	11/289 (12.2%)	7/289 (8.8%)
	Missing or undefined	0	0	0
WEEK 12	Dry	231/288 (80.2%)	202/283 (71.4%)	216/285 (75.8%)
	Not Dry	57/288 (19.8%)	81/283 (28.6%)	69/285 (24.2%)
	IRF and SRF	2/288 (3.5%)	2/283 (2.5%)	1/285 (1.4%)
	IRF only	50/288 (87.7%)	77/283 (95.1%)	67/285 (97.1%)
	SRF only	5/288 (8.8%)	2/283 (2.5%)	1/285 (1.4%)
	Missing or undefined	0	0	0
WEEK 16	Dry	231/281 (82.2%)	180/280 (64.3%)	224/281 (79.7%)
	Not Dry	50/281 (17.8%)	100/280 (35.7%)	57/281 (20.3%)
	IRF and SRF	3/281 (6.0%)	16/280 (16.0%)	1/281 (1.8%)
	IRF only	47/281 (94.0%)	84/280 (84.0%)	56/281 (98.2%)
	SRF only	0/281	0/280	0/281
	Missing or undefined	0	0	0
WEEK 20	Dry	221/276 (80.1%)	211/278 (75.9%)	221/271 (81.5%)
	Not Dry	55/276 (19.9%)	67/278 (24.1%)	50/271 (18.5%)
	IRF and SRF	1/276 (1.8%)	1/278 (1.5%)	1/271 (2.0%)
	IRF only	54/276 (98.2%)	65/278 (97.0%)	49/271 (98.0%)
	SRF only	0/276	1/278 (1.5%)	0/271
	Missing or undefined	0	0	0
WEEK 24	Dry	222/276 (80.4%)	193/271 (71.2%)	189/271 (69.7%)
	Not Dry	54/276 (19.6%)	78/271 (28.8%)	82/271 (30.3%)
	IRF and SRF	1/276 (1.9%)	7/271 (9.0%)	4/271 (4.9%)
	IRF only	53/276 (98.1%)	71/271 (91.0%)	77/271 (93.9%)
	SRF only	0/276	0/271	1/271 (1.2%)
	Missing or undefined	0	0	0
WEEK 28	Dry	220/268 (82.1%)	208/268 (77.6%)	218/264 (82.6%)
	Not Dry	48/268 (17.9%)	60/268 (22.4%)	46/264 (17.4%)
	IRF and SRF	2/268 (4.2%)	0/268	0/264
	IRF only	46/268 (95.8%)	60/268 (100.0%)	45/264 (97.8%)
	SRF only	0/268	0/268	1/264 (2.2%)
	Missing or undefined	0	0	0
WEEK 32	Dry	224/269 (83.3%)	185/264 (70.1%)	192/257 (74.7%)
	Not Dry	45/269 (16.7%)	79/264 (29.9%)	65/257 (25.3%)
	IRF and SRF	1/269 (2.2%)	4/264 (5.1%)	1/257 (1.5%)
	IRF only	44/269 (97.8%)	75/264 (94.9%)	64/257 (98.5%)
	SRF only	0/269	0/264	0/257
	Missing or undefined	0	0	0

Visit	Fluid status	2q4 (N=301) Num/Den (%)	8q8/3 (N=293) Num/Den (%)	8q8/5 (N=298) Num/Den (%)
WEEK 36	Dry	221/264 (83.7%)	211/260 (81.2%)	202/247 (81.8%)
	Not Dry	43/264 (16.3%)	49/260 (18.8%)	45/247 (18.2%)
	IRF and SRF	4/264 (9.3%)	0/260	0/247
	IRF only	39/264 (90.7%)	49/260 (100.0%)	45/247 (100.0%)
	SRF only	0/264	0/260	0/247
	Missing or undefined	0	0	1
	Both missing or undetermined	0	0	1
	IRF missing or undetermined (and SRF=No)	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0

ICE = Intercurrent Event; IRF = Intraretinal fluid; SRF = Subretinal fluid
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
No imputation of missing values after occurrence of ICEs was done.
Dry = defined as no IRF and no SRF in central subfield detected; Not dry = defined as IRF and/or SRF in central subfield detected.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 53: Time to fluid-free retina over week 36 (full analysis set)

	2q4 (N=301)	8q8/3 (N=293)	8q8/5 (N=298)
Kaplan-Meier estimated time to fluid-free retina, using			
Number of events	270	256	263
Number of censored participants	29	37	35
Median (95% CI) (weeks)	4.0 (NE,NE)	4.0 (4.0,8.0)	4.0 (NE,NE)
Q1, Q3 (weeks)	4.0, 8.0	4.0, 12.0	4.0, 12.0
Estimated event rate at Week 36	0.9246	0.8861	0.9028
Hazard ratio (a)		0.8894	0.9403
p-value (b)		0.0631	0.3232

BCVA = Best corrected visual acuity; IRF = Intraretinal fluid; NE = Not evaluable; RVO = Retinal vein occlusion; SRF = Subretinal fluid
Time to fluid-free retina is defined as the time from randomization to the time where a participant did not have any IRF or SRF in the central subfield for the first time as found in the SD-OCT (regardless of whether any retinal fluid was found again after that). Time to fluid-free retina was analysed using the Kaplan-Meier method, using the study visits (i.e. multiples of 4 weeks) and not the calendar time as unit. Intercurrent events (ICE) were handled according to primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
(a) Hazard ratio was calculated using a stratified Cox proportional hazards model model comparing 8mg groups vs. 2mg, including geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.>=60], and RVO type [CRVO/HRVO vs BRVO] as strata.
(b) p-value was calculated using a stratified log-rank test comparing 8mg groups vs. 2mg, including geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.>=60], and RVO type [CRVO/HRVO vs BRVO]) as strata.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 54: Time to IRF-free retina over week 36 (full analysis set)

	2q4 (N=301)	8q8/3 (N=293)	8q8/5 (N=298)
Kaplan-Meier estimated time to IRF-free retina, using			
Number of events	268	256	261
Number of censored participants	27	33	30
Median (95% CI) (weeks)	4.0 (NE,NE)	4.0 (NE,NE)	4.0 (NE,NE)
Q1, Q3 (weeks)	4.0, 8.0	4.0, 8.0	4.0, 8.0
Estimated event rate at Week 36	0.9271	0.8940	0.9142
Hazard ratio (a)		0.9315	0.9768
p-value (b)		0.1947	0.6605

BCVA = Best corrected visual acuity; IRF = Intraretinal fluid; NE = Not evaluable; RVO = Retinal vein occlusion
Time to IRF-free retina is defined as the time from randomization to the time where a participant did not have any IRF in the central subfield for the first time as found in the SD-OCT (regardless of whether any retinal fluid was found again after that). Time to IRF-free retina was analysed using the Kaplan-Meier method, using the study visits (i.e. multiples of 4 weeks) and not the calendar time as unit. Intercurrent events (ICE) were handled according to primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
(a) Hazard ratio was calculated using a stratified Cox proportional hazards model model comparing 8mg groups vs. 2mg, including geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.>=60], and RVO type [CRVO/HRVO vs BRVO] as strata.
(b) p-value was calculated using a stratified log-rank test comparing 8mg groups vs. 2mg, including geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.>=60], and RVO type [CRVO/HRVO vs BRVO]) as strata.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 55: Time to SRF-free retina over week 36 (full analysis set)

	2q4 (N=301)	8q8/3 (N=293)	8q8/5 (N=298)
Kaplan-Meier estimated time to SRF-free retina, using			
Number of events	182	208	200
Number of censored participants	2	1	2
Median (95% CI) (weeks)	4.0 (NE,NE)	4.0 (NE,NE)	4.0 (NE,NE)
Q1, Q3 (weeks)	4.0, 8.0	4.0, 8.0	4.0, 8.0
Estimated event rate at Week 36	1.0000	1.0000	1.0000
Hazard ratio (a)		0.9441	0.9937
p-value (b)		0.2898	0.9268

BCVA = Best corrected visual acuity; NE = Not evaluable; RVO = Retinal vein occlusion; SRF = Subretinal fluid
Time to SRF-free retina is defined as the time from randomization to the time where a participant did not have any SRF in the central subfield for the first time as found in the SD-OCT (regardless of whether any retinal fluid was found again after that). Time to SRF-free retina was analysed using the Kaplan-Meier method, using the study visits (i.e. multiples of 4 weeks) and not the calendar time as unit. Intercurrent events (ICE) were handled according to primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
(a) Hazard ratio was calculated using a stratified Cox proportional hazards model model comparing 8mg groups vs. 2mg, including geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.>=60], and RVO type [CRVO/HRVO vs BRVO] as strata.
(b) p-value was calculated using a stratified log-rank test comparing 8mg groups vs. 2mg, including geographic region [Japan vs. APAC vs. Europe vs. America], baseline BCVA [<60 vs.>=60], and RVO type [CRVO/HRVO vs BRVO]) as strata.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Based on the results provided by the Applicant, no clinically relevant differences were observed between treatment groups.

However, a borderline result was noted for time to fluid-free retina at Week 36 in the 8q8/3 treatment group, with a p-value of 0.0631 (Table 51). In light of this finding, the Applicant was requested to provide the analysis using the OC (Observed Case) approach, excluding values after intercurrent events (ICE), rather than based on the FAS population as presented in Table 51. Furthermore, to

clarify these results, the Applicant is invited to provide subgroup analyses according to the therapeutic indication (BRVO, CRVO/HRVO).

The Applicant clarified that the analysis was performed using the 'OC excluding values after ICE' approach and concluded that the numerical differences observed between the 2q4 and 8q8/3 arms are not clinically meaningful. This conclusion is considered acceptable.

Moreover, the data provided by the Applicant suggest that there is no clinically meaningful difference in the time-to-event analyses for retinal fluid status up to Week 36, either by RVO type and by treatment group.

- ***Proportion of participants having sustained fluid-free retina over 36 weeks (total fluid, IRF, and/or SRF in the central subfield)***

Table 56: Proportion of participants with sustained fluid-free retina at week 36, OC excluding values after ICE (full analysis set)

	2q4 (N=301)	8q8/3 (N=293)	8q8/5 (N=298)
Participants with sustained fluid-free retina Num/Den (%)	210/264 (79.5%)	176/259 (68.0%)	179/248 (72.2%)

ICE = Intercurrent Event; IRF = Intraretinal fluid; SRF = Subretinal fluid
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
Sustained fluid-free retina over week 36: is defined by having no IRF or SRF in the central subfield at 2 consecutive visits, and at all subsequent study visits.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 57: Proportion of participants with sustained IRF-free retina at week 36, OC excluding values after ICE (full analysis set)

	2q4 (N=301)	8q8/3 (N=293)	8q8/5 (N=298)
Participants with sustained IRF-free retina Num/Den (%)	210/264 (79.5%)	176/259 (68.0%)	179/248 (72.2%)

ICE = Intercurrent Event; IRF = Intraretinal fluid
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
Sustained IRF-free retina over week 36: is defined by having no IRF in the central subfield at 2 consecutive visits, and at all subsequent study visits.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 58: Proportion of participants with sustained SRF-free retina at week 36, OC excluding values after ICE (full analysis set)

	2q4 (N=301)	8q8/3 (N=293)	8q8/5 (N=298)
Participants with sustained SRF-free retina Num/Den (%)	260/264 (98.5%)	255/259 (98.5%)	246/248 (99.2%)

ICE = Intercurrent Event; SRF = Subretinal fluid
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
Sustained SRF-free retina over week 36: is defined by having no SRF in the central subfield at 2 consecutive visits, and at all subsequent study visits.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 59: QUASAR: Retinal fluid status at Week 36 by RVO type

OC excluding values after ICE (full analysis set)

Number (%) of participants	BRVO / CRVO/HRVO	2q4 Num/Den (%) BRVO (N=149) / CRVO/HRVO (N=152)	8q8/3 Num/Den (%) BRVO (N=159) / CRVO/HRVO (N=134)	8q8/5 Num/Den (%) BRVO (N=159) / CRVO/HRVO (N=139)
Sustained fluid-free retina	**BRVO**	99/131 (75.6%)	93/140 (66.4%)	86/134 (64.2%)
Source: Post-hoc table 1.2/9	**CRVO/HRVO**	111/133 (83.5%)	83/119 (69.7%)	93/114 (81.6%)
Sustained IRF-free retina	**BRVO**	99/131 (75.6%)	93/140 (66.4%)	86/134 (64.2%)
Source: Post-hoc table 1.2/11	**CRVO/HRVO**	111/133 (83.5%)	83/119 (69.7%)	93/114 (81.6%)
Sustained SRF-free retina	**BRVO**	129/131 (98.5%)	137/140 (97.9%)	134/134 (100.0%)
Source: Post-hoc table 1.2/13	**CRVO/HRVO**	131/133 (98.5%)	118/119 (99.2%)	112/114 (98.2%)

ICE = intercurrent event; IRF = intraretinal fluid; RVO = retinal vein occlusion; SRF = subretinal fluid
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
Sustained fluid-free retina over Week 36: is defined by having no IRF or SRF in the central subfield at 2 consecutive visits, and at all subsequent study visits.

A numerically higher proportion of participants in the 2q4 group (79.5%) demonstrated a sustained fluid-free retina (defined as no IRF or SRF) compared to the 8q8/3 group (68.0%) and the 8q8/5 group (72.2%), with all values prior to ICE. A sustained IRF-free retina at Week 36 was observed in a numerically higher proportion of participants in the 2q4 group (79.5%) compared to the HD groups (68.8% and 72.2%). Separately, a high (>98.5%) and consistent proportion of participants across all three treatment groups achieved a sustained SRF-free retina.

The Applicant provided data by RVO subtype, showing a numerically higher efficacy for the 2q4 regimen in achieving a sustained fluid-free retina among participants with either BRVO or CRVO/HRVO, compared with the 8q8/3 and 8q8/5 regimens. However, these differences are not statistically significant.

- ***Change in area of retinal ischemia at Week 36***

Table 60: Summary statistics for change in area of retinal ischemia (mm2) at week 36, OC excluding values after ICE (full analysis set)

		Value at Visit						Change from Baseline					
Treatment	Visit	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max
2q4 (N=301)	BASELINE	257	4.20 (4.80)	0.30	2.90	0.00, 7.75	0.0, 28.1						
	WEEK 12	265	4.12 (4.29)	0.26	3.32	0.00, 7.19	0.0, 24.9	227	0.08 (3.60)	0.24	0.00	-0.97, 0.60	-13.0, 24.1
	WEEK 36	254	4.80 (5.52)	0.35	3.85	0.00, 7.92	0.0, 49.3	218	0.67 (5.58)	0.38	0.00	-0.94, 1.82	-17.8, 49.3
8q8/3 (N=293)	BASELINE	247	4.68 (4.83)	0.31	3.91	0.00, 7.73	0.0, 26.9						
	WEEK 12	268	4.75 (4.73)	0.29	4.30	0.00, 8.13	0.0, 27.5	230	-0.04 (3.77)	0.25	0.00	-1.13, 1.00	-21.6, 18.7
	WEEK 36	248	5.21 (5.11)	0.32	4.52	0.00, 8.63	0.0, 26.6	208	0.30 (4.86)	0.34	0.00	-1.23, 1.85	-22.7, 17.2
8q8/5 (N=298)	BASELINE	250	4.64 (4.91)	0.31	3.26	0.00, 8.08	0.0, 24.2						
	WEEK 12	264	4.48 (4.58)	0.28	3.34	0.00, 7.63	0.0, 25.0	226	0.04 (4.07)	0.27	0.00	-1.38, 0.77	-17.1, 25.0
	WEEK 36	239	4.64 (4.37)	0.28	4.50	0.00, 7.85	0.0, 21.9	199	-0.38 (4.25)	0.30	0.00	-2.14, 1.20	-16.4, 15.7

ICE = Intercurrent Event
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 61: Number of participants with retinal ischemia (perifoveal and parafoveal ischemia, non-perfusion outside the macula) by FA - study eye (safety analysis set)

Visit	Category		2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
BASELINE	Presence of Perifoveal and Parafoveal Ischemia (in the 6 mm ETDRS Grid)	Missing	23 (7.6%)	14 (4.8%)	22 (7.4%)	36 (6.1%)
		No	72 (23.9%)	56 (19.1%)	62 (20.8%)	118 (20.0%)
		Yes	178 (59.1%)	199 (67.9%)	185 (62.1%)	384 (65.0%)
		Undetermined	28 (9.3%)	24 (8.2%)	29 (9.7%)	53 (9.0%)
	Presence of Retinal Area of Non-perfusion Outside the Macula	Missing	13 (4.3%)	11 (3.8%)	13 (4.4%)	24 (4.1%)
		No	72 (23.9%)	67 (22.9%)	64 (21.5%)	131 (22.2%)
		Yes	189 (62.8%)	197 (67.2%)	193 (64.8%)	390 (66.0%)
		Undetermined	27 (9.0%)	18 (6.1%)	28 (9.4%)	46 (7.8%)
WEEK 12	Presence of Perifoveal and Parafoveal Ischemia (in the 6 mm ETDRS Grid)	Missing	31 (10.3%)	21 (7.2%)	30 (10.1%)	51 (8.6%)
		No	76 (25.2%)	65 (22.2%)	65 (21.8%)	130 (22.0%)
		Yes	175 (58.1%)	188 (64.2%)	189 (63.4%)	377 (63.8%)
		Undetermined	19 (6.3%)	19 (6.5%)	14 (4.7%)	33 (5.6%)
	Presence of Retinal Area of Non-perfusion Outside the Macula	Missing	27 (9.0%)	22 (7.5%)	28 (9.4%)	50 (8.5%)
		No	74 (24.6%)	70 (23.9%)	60 (20.1%)	130 (22.0%)
		Yes	170 (56.5%)	184 (62.8%)	191 (64.1%)	375 (63.5%)
		Undetermined	30 (10.0%)	17 (5.8%)	19 (6.4%)	36 (6.1%)
WEEK 36	Presence of Perifoveal and Parafoveal Ischemia (in the 6 mm ETDRS Grid)	Missing	31 (10.3%)	33 (11.3%)	44 (14.8%)	77 (13.0%)
		No	76 (25.2%)	66 (22.5%)	68 (22.8%)	134 (22.7%)
		Yes	178 (59.1%)	178 (60.8%)	173 (58.1%)	351 (59.4%)
		Undetermined	16 (5.3%)	16 (5.5%)	13 (4.4%)	29 (4.9%)
	Presence of Retinal Area of Non-perfusion Outside the Macula	Missing	29 (9.6%)	33 (11.3%)	44 (14.8%)	77 (13.0%)
		No	85 (28.2%)	70 (23.9%)	66 (22.1%)	136 (23.0%)
		Yes	168 (55.8%)	175 (59.7%)	174 (58.4%)	349 (59.1%)
		Undetermined	19 (6.3%)	15 (5.1%)	14 (4.7%)	29 (4.9%)

FA = Fluorescein angiography assessment
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.
All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals.

Table 62: Change from baseline in area of retinal ischemia at Week 36 by RVO type

	2q4	8q8/3	8q8/5
BRVO	(N=149)	(N=159)	(N=159)
	0.44 (3.17)	0.73 (4.15)	-0.12 (3.78)
CRVO/HRVO	(N=152)	(N=134)	(N=139)
	0.90 (7.26)	-0.19 (5.55)	-0.71 (4.78)

ICE = Intercurrent Event; RVO = Retinal vein occlusion
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.

The mean (SD) change in retinal ischemia area from baseline to Week 36 was 0.30 (4.86) mm² in the 8q8/3 group and -0.38 (4.25) mm² in the 8q8/5 group, compared to 0.67 (5.58) mm² in the 2q4 group. These figures exclude values obtained after ICE, and the observed differences across the treatment groups were not considered clinically meaningful. Thus, it is observed a higher efficacy concerning the 8q8/3 group comparing to the 8q8/5 group.

Moreover, according to Table 59, the presence of perifoveal and parafoveal ischemia was not well balanced across the treatment groups at baseline. Specifically, 178 (59.1%) participants in the 2q4 group, 199 (67.9%) in the 8q8/3 group, and 185 (62.1%) in the 8q8/5 group presented with this condition at baseline.

It is well recognized that both the extent (area) and location of retinal ischemia vary among patients with RVO. Moreover, grading ischemia can be challenging in the presence of dense intraretinal haemorrhages, which are more frequent in CRVO/HRVO. Additionally, baseline areas of ischemia were generally larger in the BRVO patient population compared to the CRVO/HRVO population.

The observed results are difficult to interpret and cannot support any conclusions regarding the efficacy of high- or low-dose treatment. Furthermore, the heterogeneity between RVO subtypes and the fact that patients were not randomized across the three treatment groups prevent any conclusions regarding changes in the area of retinal ischemia.

Thus, in light of this interpretation and given that this is an exploratory endpoint, no further action is warranted regarding this question.

- ***Change in the area of fluorescein leakage at Week 36***

Table 63: Summary statistics for change in area of fluorescein leakage (mm2) at week 36, OC excluding values after ICE (full analysis set)

		Value at Visit						Change from Baseline					
Treatment	Visit	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max
2q4 (N=301)	BASELINE	298	11.22 (7.16)	0.41	9.38	6.20, 14.20	0.0, 55.1						
	WEEK 12	269	1.88 (3.66)	0.22	0.00	0.00, 2.30	0.0, 27.1	266	-9.49 (7.53)	0.46	-7.96	-13.00, -4.31	-55.1, 6.6
	WEEK 36	255	1.19 (3.07)	0.19	0.00	0.00, 0.67	0.0, 27.9	253	-10.35 (7.66)	0.48	-8.62	-13.40, -5.10	-55.1, 3.6
8q8/3 (N=293)	BASELINE	287	10.57 (6.25)	0.37	9.34	6.30, 13.26	0.0, 56.5						
	WEEK 12	266	1.66 (3.14)	0.19	0.00	0.00, 1.90	0.0, 24.9	265	-8.91 (6.30)	0.39	-8.10	-11.40, -4.93	-56.5, 7.3
	WEEK 36	245	0.79 (1.67)	0.11	0.00	0.00, 0.70	0.0, 9.0	242	-10.02 (6.39)	0.41	-9.00	-12.60, -5.70	-56.5, 3.9
8q8/5 (N=298)	BASELINE	288	10.78 (6.19)	0.36	9.35	6.31, 13.53	0.0, 28.4						
	WEEK 12	268	1.47 (2.70)	0.17	0.00	0.00, 1.82	0.0, 23.0	262	-9.48 (6.37)	0.39	-8.28	-12.30, -4.89	-28.4, 6.1
	WEEK 36	235	0.82 (1.82)	0.12	0.00	0.00, 0.60	0.0, 10.9	229	-10.43 (6.47)	0.43	-8.95	-13.40, -6.10	-28.4, 9.2

ICE = Intercurrent Event
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

Table 64: Number of participants with macular leakage by FA - study eye (safety analysis set)

Visit	Category	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
BASELINE	Missing	1 (0.3%)	2 (0.7%)	6 (2.0%)	8 (1.4%)
	No	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
	Yes	296 (98.3%)	289 (98.6%)	289 (97.0%)	578 (97.8%)
	Undetermined	2 (0.7%)	0	0	0
WEEK 12	Missing	29 (9.6%)	25 (8.5%)	28 (9.4%)	53 (9.0%)
	No	114 (37.9%)	120 (41.0%)	126 (42.3%)	246 (41.6%)
	Yes	135 (44.9%)	124 (42.3%)	126 (42.3%)	250 (42.3%)
	Undetermined	23 (7.6%)	24 (8.2%)	18 (6.0%)	42 (7.1%)
WEEK 36	Missing	31 (10.3%)	38 (13.0%)	46 (15.4%)	84 (14.2%)
	No	153 (50.8%)	150 (51.2%)	147 (49.3%)	297 (50.3%)
	Yes	100 (33.2%)	93 (31.7%)	92 (30.9%)	185 (31.3%)
	Undetermined	17 (5.6%)	12 (4.1%)	13 (4.4%)	25 (4.2%)

FA = Fluorescein angiography assessment
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.
All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals.

Table 65: QUASAR: Change from baseline in leakage area at Week 36 by RVO type

Results expressed as mean (SD) changes in area of fluorescein leakage (mm^2).
OC excluding values after ICE (full analysis set)

	2q4	8q8/3	8q8/5
BRVO	(N=149)	(N=159)	(N=159)
	-6.34 (4.03)	-7.66 (5.53)	-7.73 (3.54)
CRVO/HRVO	(N=152)	(N=134)	(N=139)
	-14.46 (8.31)	-12.85 (6.22)	-13.86 (7.63)

ICE = Intercurrent Event; RVO = Retinal vein occlusion
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.

The mean (SD) reduction in fluorescein leakage area from baseline to Week 36 was -10.02 (6.39) mm^2 in the 8q8/3 group, -10.43 (6.47) mm^2 in the 8q8/5 group, and -10.35 (7.66) mm^2 in the 2q4 group. These reductions appear similar across all treatment groups, and, importantly, the differences were not considered clinically meaningful. However, to be in line with the clinical indication, the Applicant was invited to provide these data by subgroup analyses by RVO type.

The Applicant argued that, as with retinal ischemia area, the extent of macular fluorescein leakage varies by RVO type and is highly case-dependent, influenced by factors similar to those affecting retinal ischemia. The extent of leakage was not considered during stratification or randomization. Overall, the baseline leakage area is higher in the CRVO/HRVO patient population, which is expected due to the location of the occlusion and its associated sequelae.

When comparing efficacy by RVO subtype and treatment, numerical differences were observed.

For BRVO, the high-dose regimens (8q8/3: -7.66 [5.53] mm²; 8q8/5: -7.73 [3.54] mm²) showed slightly greater reductions in fluorescein leakage area compared with the 2q4 regimen (-6.34 [4.03] mm²).

For CRVO/HRVO, the lower-dose 2q4 regimen (-14.46 [8.31] mm²) demonstrated slightly greater reductions than the high-dose regimens (8q8/3: -12.85 [6.22] mm²; 8q8/5: -13.86 [7.63] mm²).

Overall, these data are consistent across treatment groups, and the observed numerical differences are not considered clinically meaningful.

The observed results for macular leakage appear to be similar across treatments and RVO subtypes.

– Subgroup analyses for the primary efficacy variable

○ *Subgroup analyses for the primary efficacy variable*

Table 66: Treatment group comparison: 8q8/3 vs 2q4

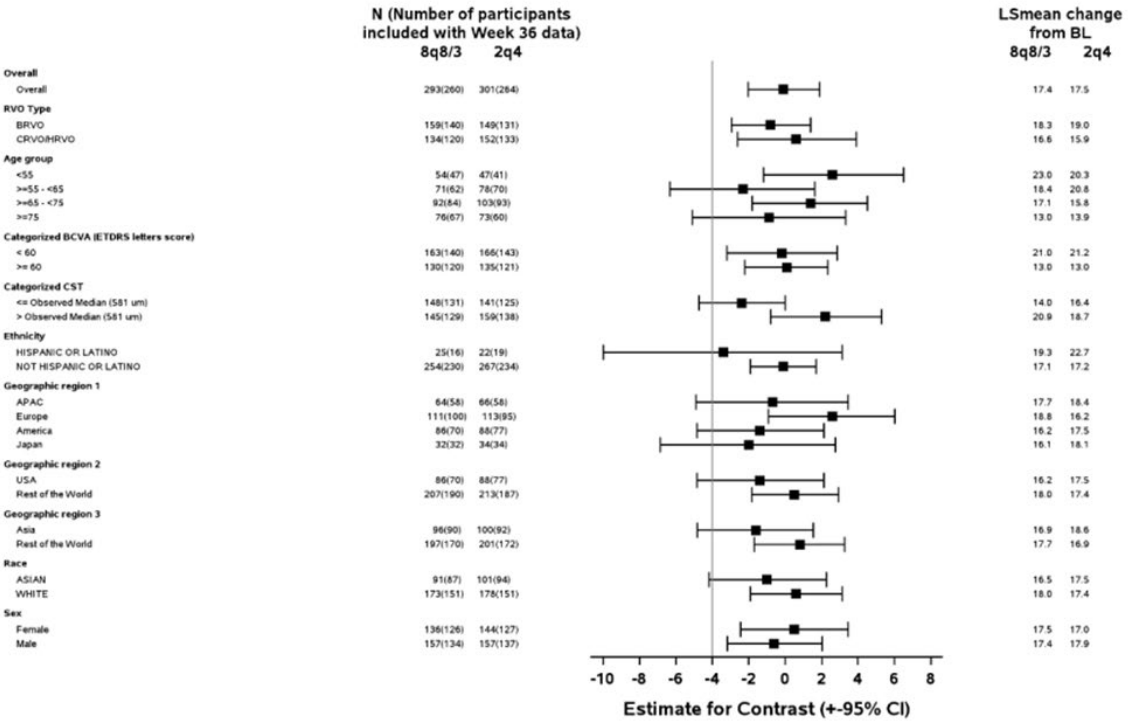
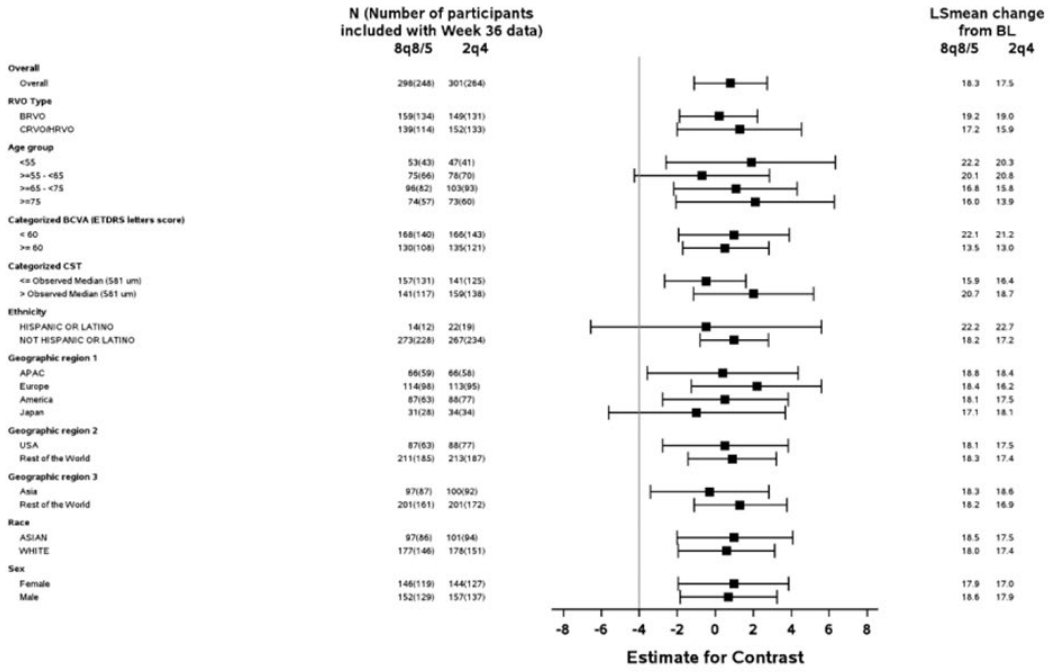


Table 67: Treatment group comparison: 8q8/5 vs 2q4



APAC = Asia-Pacific; BCVA = best-corrected visual acuity; ETDRS = early treatment diabetic retinopathy study; ; ICE = intercurrent events; LS = least squares; MMRM = mixed model for repeated measurements; RVO = retinal vein occlusion

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

For subgroup analysis based on geographic regions, baseline BCVA and RVO type, the corresponding variable was excluded from the statistical models.

ICEs were handled according to primary estimand strategy as described in Table 4-2 of the SAP Section 4.2.2.1 in CRS Section 10.1.9.

See Definition of terms for treatment group description.

Subgroup analyses show results consistent with the overall result. Of note the better homogeneity of subgroups for the 8 mg/5 arm for which almost all subgroups (88%=21/24) achieve the non-inferiority despite their smaller size.

- ***Subgroup analyses by RVO type***

Table 68: Change from baseline in BCVA measured by the ETDRS letter score at week 36, MMRM by RVO type (full analysis set)

RVO Type	BRVO			CRVO/HRVO		
	2q4 N = 149	8q8/3 N = 159	8q8/5 N = 159	2q4 N = 152	8q8/3 N = 134	8q8/5 N = 139
Baseline mean [a]	57.3	58.6	58.5	51.0	51.3	51.8
Number of participants with Week 36 data (included/excluded due to ICE)	131/8	140/5	134/11	133/9	120/7	114/7
Arithmetic mean (SD) change from baseline [a]	19.4 (11.0)	17.4 (10.9)	19.5 (10.0)	16.2 (14.7)	16.5 (12.7)	18.6 (12.6)
LS mean (SE) change from baseline	19.0 (0.8)	18.3 (0.8)	19.2 (0.7)	15.9 (1.2)	16.6 (1.1)	17.2 (1.2)
Contrast [b]		8q8/3 - 2q4	8q8/5 - 2q4		8q8/3 - 2q4	8q8/5 - 2q4
Estimate for contrast and two-sided 95% CI [c]		-0.8 (-2.9, 1.4)	0.2 (-1.9, 2.2)		0.6 (-2.6, 3.9)	1.3 (-2.0, 4.5)
Nominal p-value of one-sided test for non-inferiority at a margin of 4 letters		0.0018	<.0001		0.0027	0.0008

APAC = Asia-Pacific; BCVA = best-corrected visual acuity; CI = Confidence Interval; ETDRS = early treatment diabetic retinopathy study; ICE = intercurrent events; LS = least-squares; MMRM = mixed model for repeated measurements; RVO = retinal vein occlusion; SD = Standard Deviation; SE = Standard Error.

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

ICEs were handled according to primary estimand strategy as described in Table 4-2 of the SAP Section 4.2.2.1 in CRS Section 10.1.9.

(a) based on observed cases excluding data after ICE.

(b) The contrast also includes the interaction term for treatment x visit (at week 36, for details on the population-level summary see SAP Section 4.2.2 in CSR Section 10.1.9).

(c) Estimate based on the MMRM, was computed for the differences of 8q8/3 minus 2q4 and 8q8/5 minus 2q4, respectively with two-sided 95% CIs.

See Definition of terms for treatment group description.

For participants with BRVO, the differences in LS mean changes (95% confidence intervals) were -0.8 letters (-2.9 to 1.4) for 8q8/3 compared to 2q4, and 0.2 letters (-1.9 to 2.2) for 8q8/5 versus 2q4. In the CRVO/HRVO group, the corresponding differences were 0.6 letters (-2.6 to 3.9) for 8q8/3 versus 2q4, and 1.3 letters (-2.0 to 4.5) for 8q8/5 versus 2q4. In both RVO subtypes, these results were aligned with those observed in the pooled RVO population and fulfilled the predefined non-inferiority criteria, as the lower bound of the 95% confidence interval remained above -4.

– Subgroup analyses for the secondary efficacy variable

○ *Number of active injections from baseline to Week 36 by RVO type*

Table 69:Number of active injections from baseline to Week 36, Main Analysis by RVO type (full analysis set)

RVO Type	Treatment	LS mean (SE) number of active injections (a)	Contrast	Estimate for contrast and two-sided 95% CI (a)	p-value (b)
BRVO	8q8/3 (N=159)	6.1 (0.0)	8q8/3 - 2q4	-2.7 (-2.9, -2.6)	<.0001
	8q8/5 (N=159)	6.9 (0.0)	8q8/5 - 2q4	-1.9 (-2.0, -1.8)	<.0001
	2q4 (N=149)	8.8 (0.1)			
CRVO/HRVO	8q8/3 (N=134)	6.1 (0.0)	8q8/3 - 2q4	-2.6 (-2.8, -2.5)	<.0001
	8q8/5 (N=139)	6.9 (0.0)	8q8/5 - 2q4	-1.8 (-1.9, -1.6)	<.0001
	2q4 (N=152)	8.7 (0.1)			

CI = Confidence Interval; LS = Least Square; SE = Standard Error
Missing endpoint values were imputed using a multiple imputation approach as described in Section 4.3.1.2 of the SAP.
A non-parametric rank analysis of covariance (ANCOVA) was used on each imputed dataset, adjusting for baseline BCVA, baseline CST, and the stratification variables (geographic region [Japan + APAC vs. Europe vs. America] and BCVA score [<60 vs. >=60]) and results were combined using Rubin's rule.
Intercurrent events were handled according to the secondary estimand strategy as described in Table 4-6 in Section 4.3.1.3 of the SAP.
(a) Based on the application of Rubin's rule after fitting a linear regression model adjusted for the same covariates as the non-parametric rank ANCOVA on each imputed dataset.
(b) p-value based on the non-parametric rank ANCOVA applied to each imputed dataset and combined using Rubin's rule.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

The LS mean number of active injections from baseline to Week 36 was comparable across the 2q4, 8q8/3, and 8q8/5 groups, with values of 8.8, 6.1, and 6.9, respectively, in participants with BRVO, and 8.7, 6.1, and 6.9, respectively, in those with CRVO/HRVO.

- ***Change from baseline in CST at Week 36 by RVO type***

Table 70: Summary statistics for CST (um) by RVO Type and visit, OC excluding values after ICE (full analysis set) - BRVO

			Value at Visit						Change from Baseline					
RVO Type	Treatment	Visit	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max
BRVO	2q4 (N=149)	BASELINE	149	552.6 (169.8)	13.9	545.0	422.0, 630.0	302, 1036						
		WEEK 4	146	284.8 (69.3)	5.7	272.5	244.0, 299.0	194, 662	146	-265.5 (177.0)	14.6	-254.0	-360.0, -150.0	-835, 246
		WEEK 8	144	268.9 (57.3)	4.8	259.0	236.5, 285.0	186, 560	144	-278.5 (176.9)	14.7	-265.5	-372.0, -153.0	-843, 127
		WEEK 12	139	265.5 (49.8)	4.2	257.0	235.0, 287.0	182, 477	139	-283.9 (175.3)	14.9	-269.0	-381.0, -154.0	-740, 72
		WEEK 16	137	265.1 (51.0)	4.4	256.0	234.0, 282.0	177, 467	137	-286.4 (182.8)	15.6	-266.0	-370.0, -157.0	-832, 120
		WEEK 20	137	261.4 (47.0)	4.0	253.0	233.0, 278.0	177, 494	137	-293.8 (181.4)	15.5	-277.0	-392.0, -155.0	-833, -4
		WEEK 24	136	261.4 (49.5)	4.2	255.5	231.0, 279.5	181, 460	136	-290.6 (181.8)	15.6	-277.0	-382.0, -154.0	-834, 134
		WEEK 28	131	260.3 (48.7)	4.3	255.0	231.0, 277.0	183, 516	131	-294.3 (181.6)	15.9	-276.0	-380.0, -162.0	-838, 71
		WEEK 32	133	259.4 (47.4)	4.1	253.0	231.0, 277.0	182, 444	133	-294.4 (183.5)	15.9	-278.0	-375.0, -160.0	-849, 110
		WEEK 36	131	257.9 (44.5)	3.9	252.0	230.0, 277.0	180, 418	131	-295.8 (183.0)	16.0	-280.0	-386.0, -156.0	-850, 74
	8q8/3 (N=159)	BASELINE	159	548.8 (170.2)	13.5	527.0	422.0, 642.0	272, 1008						
		WEEK 4	158	280.6 (49.6)	3.9	274.5	255.0, 300.0	187, 515	158	-265.7 (172.7)	13.7	-234.0	-365.0, -133.0	-774, 28
		WEEK 8	158	267.3 (50.9)	4.1	263.0	239.0, 285.0	170, 512	158	-281.9 (183.3)	14.6	-248.0	-379.0, -137.0	-788, 6
		WEEK 12	153	265.0 (47.4)	3.8	262.0	236.0, 282.0	169, 508	153	-277.7 (181.4)	14.7	-251.0	-362.0, -144.0	-794, 10
		WEEK 16	151	287.0 (88.9)	7.2	264.0	239.0, 297.0	167, 783	151	-258.1 (179.5)	14.6	-226.0	-357.0, -127.0	-794, 63
		WEEK 20	150	262.8 (50.5)	4.1	258.0	233.0, 284.0	168, 530	150	-282.9 (180.3)	14.7	-254.0	-381.0, -157.0	-798, 2
		WEEK 24	148	275.0 (75.7)	6.2	261.5	236.5, 289.0	164, 717	148	-268.1 (187.4)	15.4	-239.0	-373.5, -134.0	-791, 445
		WEEK 28	146	260.0 (52.2)	4.3	253.5	233.0, 275.0	163, 583	146	-288.0 (180.6)	14.9	-256.5	-388.0, -162.0	-793, 12
		WEEK 32	144	269.0 (70.4)	5.9	258.0	236.5, 282.5	166, 765	144	-275.7 (185.3)	15.4	-239.0	-383.5, -140.5	-794, 194
		WEEK 36	140	262.3 (64.8)	5.5	255.0	232.0, 271.5	161, 804	140	-284.1 (183.1)	15.5	-252.0	-386.5, -162.5	-797, 233
	8q8/5 (N=159)	BASELINE	159	540.6 (161.4)	12.8	506.0	428.0, 633.0	268, 1160						
		WEEK 4	156	283.2 (45.5)	3.6	277.5	253.0, 305.0	202, 537	156	-256.4 (161.9)	13.0	-231.0	-352.5, -134.5	-911, -26
		WEEK 8	155	268.8 (39.3)	3.2	267.0	242.0, 294.0	155, 390	155	-269.1 (167.9)	13.5	-237.0	-362.0, -146.0	-930, -13
		WEEK 12	152	265.2 (38.1)	3.1	264.0	239.5, 287.5	145, 382	152	-273.9 (168.6)	13.7	-244.5	-368.0, -148.5	-926, -24
		WEEK 16	152	264.3 (38.6)	3.1	258.5	239.5, 288.5	149, 386	152	-275.1 (168.6)	13.7	-240.0	-369.0, -150.5	-925, -22
		WEEK 20	143	260.7 (38.8)	3.2	255.0	235.0, 284.0	147, 382	143	-274.5 (165.1)	13.8	-240.0	-365.0, -150.0	-929, -21
		WEEK 24	146	269.3 (49.8)	4.1	259.5	237.0, 288.0	150, 488	146	-267.7 (170.6)	14.1	-233.0	-367.0, -146.0	-924, -6
		WEEK 28	144	260.8 (38.8)	3.2	257.0	233.0, 286.0	151, 383	144	-279.0 (169.8)	14.2	-245.0	-369.5, -155.5	-926, -20
		WEEK 32	138	263.7 (41.9)	3.6	258.0	235.0, 286.0	151, 431	138	-278.6 (172.2)	14.7	-246.0	-372.0, -158.0	-929, -12
		WEEK 36	134	261.1 (38.9)	3.4	253.0	233.0, 285.0	184, 387	134	-285.1 (171.9)	14.8	-251.5	-377.0, -165.0	-927, -8

Table 71: Summary statistics for CST (um) by RVO Type and visit, OC excluding values after ICE (full analysis set) – CRVO/HRVO

			Value at Visit						Change from Baseline					
RVO Type	Treatment	Visit	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max	n	Mean (SD)	SEM	Median	Q1, Q3	Min, Max
CRVO/HRVO	2q4 (N=152)	BASELINE	151	748.0 (259.5)	21.1	700.0	573.0, 892.0	316, 1601						
		WEEK 4	149	305.7 (91.9)	7.5	284.0	261.0, 316.0	119, 856	148	-441.1 (251.1)	20.6	-411.0	-573.5, -268.0	-1305, 11
		WEEK 8	147	271.0 (58.5)	4.8	269.0	236.0, 291.0	115, 584	146	-476.5 (274.3)	22.7	-436.5	-595.0, -297.0	-1379, -9
		WEEK 12	149	264.9 (72.8)	6.0	259.0	229.0, 282.0	47, 811	148	-484.3 (273.7)	22.5	-446.5	-598.5, -306.5	-1462, -9
		WEEK 16	144	259.4 (64.7)	5.4	256.0	228.5, 278.0	20, 667	143	-492.5 (278.8)	23.3	-447.0	-621.0, -308.0	-1459, -39
		WEEK 20	139	258.1 (69.5)	5.9	253.0	225.0, 277.0	23, 766	138	-492.1 (274.8)	23.4	-444.0	-607.0, -313.0	-1440, -37
		WEEK 24	139	262.6 (88.6)	7.5	254.0	225.0, 276.0	20, 880	138	-491.8 (280.5)	23.9	-443.0	-611.0, -313.0	-1458, -43
		WEEK 28	137	263.0 (86.1)	7.4	255.0	226.0, 276.0	17, 798	136	-487.3 (280.2)	24.0	-437.5	-605.5, -310.0	-1462, -41
		WEEK 32	136	256.9 (78.8)	6.8	248.5	223.0, 275.0	29, 816	135	-495.9 (282.8)	24.3	-446.0	-616.0, -315.0	-1443, -43
		WEEK 36	132	255.1 (80.8)	7.0	247.0	224.5, 273.5	26, 682	131	-498.8 (281.2)	24.6	-456.0	-620.0, -313.0	-1434, -44
	8q8/3 (N=134)	BASELINE	134	717.9 (257.4)	22.2	683.5	535.0, 858.0	305, 1499						
		WEEK 4	131	292.9 (50.6)	4.4	293.0	261.0, 313.0	194, 582	131	-420.3 (249.4)	21.8	-386.0	-557.0, -252.0	-1253, -35
		WEEK 8	131	272.2 (42.4)	3.7	275.0	246.0, 299.0	168, 461	131	-440.9 (259.1)	22.6	-403.0	-583.0, -252.0	-1261, -40
		WEEK 12	130	264.9 (44.3)	3.9	265.5	242.0, 292.0	161, 554	130	-447.3 (263.6)	23.1	-408.0	-578.0, -256.0	-1264, -43
		WEEK 16	129	288.0 (99.9)	8.8	270.0	240.0, 299.0	155, 793	129	-420.4 (262.2)	23.1	-384.0	-564.0, -215.0	-1212, 117
		WEEK 20	128	256.3 (35.4)	3.1	258.5	231.0, 282.5	148, 369	128	-451.7 (257.9)	22.8	-429.0	-606.5, -263.5	-1246, -40
		WEEK 24	123	261.4 (47.7)	4.3	260.0	233.0, 284.0	143, 568	123	-449.0 (261.9)	23.6	-418.0	-610.0, -256.0	-1244, -37
		WEEK 28	121	254.6 (37.8)	3.4	255.0	230.0, 281.0	142, 384	121	-462.5 (260.8)	23.7	-441.0	-631.0, -276.0	-1254, -42
		WEEK 32	120	257.9 (42.9)	3.9	255.5	230.5, 286.0	147, 392	120	-454.1 (265.3)	24.2	-437.0	-622.5, -255.0	-1250, -41
		WEEK 36	120	252.9 (37.4)	3.4	253.5	227.0, 283.0	149, 389	120	-461.2 (262.8)	24.0	-439.0	-634.0, -272.0	-1259, -38
	8q8/5 (N=139)	BASELINE	139	687.7 (237.7)	20.2	654.0	491.0, 868.0	313, 1424						
		WEEK 4	135	284.5 (36.9)	3.2	282.0	261.0, 309.0	145, 414	135	-400.2 (235.8)	20.3	-378.0	-570.0, -221.0	-1102, -26
		WEEK 8	134	271.4 (44.2)	3.8	269.0	248.0, 291.0	141, 589	134	-420.2 (239.6)	20.7	-391.5	-587.0, -231.0	-1129, -35
		WEEK 12	133	262.8 (34.0)	2.9	263.0	242.0, 284.0	133, 383	133	-421.9 (239.9)	20.8	-387.0	-595.0, -232.0	-1124, -37
		WEEK 16	129	260.7 (36.2)	3.2	260.0	240.0, 283.0	135, 384	129	-427.6 (247.4)	21.8	-386.0	-599.0, -233.0	-1152, -37
		WEEK 20	127	259.2 (38.1)	3.4	258.0	238.0, 279.0	137, 405	127	-424.1 (238.3)	21.1	-385.0	-595.0, -233.0	-1162, -37
		WEEK 24	124	279.8 (96.8)	8.7	260.0	237.5, 284.0	131, 932	124	-407.7 (262.4)	23.6	-362.5	-600.5, -205.5	-1125, 117
		WEEK 28	120	257.0 (37.4)	3.4	256.5	232.5, 276.0	128, 408	120	-426.3 (252.5)	23.0	-383.0	-603.0, -224.0	-1138, -40
		WEEK 32	118	263.7 (67.7)	6.2	255.0	231.0, 279.0	131, 731	118	-425.1 (264.6)	24.4	-385.5	-609.0, -218.0	-1142, 194
		WEEK 36	113	255.9 (37.5)	3.5	254.0	233.0, 276.0	127, 413	113	-429.0 (255.3)	24.0	-385.0	-608.0, -220.0	-1146, -38

BRVO = Branch retinal vein occlusion; CRVO = Central retinal vein occlusion; CST = Central subfield thickness; HRVO = Hemiretinal vein occlusion; ICE = Intercurrent Event; RVO = Retinal vein occlusion
OC (observed cases) excluding values after ICE (intercurrent event): observations after the occurrence of an ICE are excluded in line with the primary estimand strategy as described in Table 6-11 in Section 6.5 of the SAP.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.

A reduction in efficacy was observed at Week 16 with the 8q8/3 dosing regimen, and at Weeks 24 and 32 for both 8q8/3 and 8q8/5 regimens, when compared to the 2q4 regimen. Nevertheless, this decrease does not appear to be clinically significant.

Regarding the observed variations and the decrease in efficacy for CST at Weeks 16, 24, and 32, it is fully acknowledged that these correspond to fluctuations due to the need to increase the treatment frequency in certain patients.

EYLEA 8 mg Q4 dosing

As mentioned previously, the MAH submitted a grouped type II variation for Eylea 114.3 mg/ml to update the Product Information:

- A type II variation under category C.I.6.a has been submitted to extend the therapeutic indication to include the treatment of macular edema secondary to retinal vein occlusion (RVO), supported on the results of the pivotal Phase III study 22153 (QUASAR). Accordingly, updates have been made to sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC, and the package leaflet has been revised to reflect these changes.
- A type II variation (C.I.4) has been submitted to revise the minimum treatment interval in SmPC section 4.2 for nAMD and DME, based on data from study 22153 (QUASAR) and post-hoc analyses of studies 20968 (PULSAR), 21091 (PHOTON), and 21086 (CANDELA).

The label for high-dose aflibercept in nAMD and DME indicates that, after three monthly injections, maintenance doses should be given no more frequently than every two months. The MAH proposed to allow dosing as frequently as every 4 weeks (Q4) during the maintenance phase for the approved indications of nAMD, DME, and RVO.

The clinical trials supporting the inclusion of a Q4 dosing interval option in the aflibercept 8 mg product information for RVO, nAMD, and DME include the QUASAR, PULSAR, PHOTON, and CANDELA studies. These studies have been previously assessed, and only the specific criteria related to the new indication proposed by the Applicant are evaluated.

QUASAR (RVO): The ongoing Phase 3 QUASAR study provides efficacy and safety data through Week 36 in participants with RVO. At Week 36, efficacy data are presented for participants who, after receiving 3 to 5 initial monthly injections, either continued on a Q8 treatment interval or had their regimen shortened to Q4 based on visual and anatomic DRM criteria.

Table 72: Summary of clinical studies supporting this application (QUASAR)

Study number Report location Study status	Study population	Study design Treatment duration	Study objectives	Treatment, dose, and regimen	Data supporting this application
Macular edema secondary to retinal vein occlusion					
Study 22153 (QUASAR) Module 5.3.5.1 QUASAR W36 CSR Last participant last visit for the Week 36 primary endpoint: 07 Nov 2024 DBL (for Primary EP): 13 Dec 2024 Ongoing (Week 36 Primary endpoint completed)	Men or women ≥18 years of age with treatment-naïve macular edema involving the foveal center secondary to RVO (BRVO, HRVO or CRVO) diagnosed within 16 weeks (112 days) before the screening visit	Phase 3, multicenter, randomized, double-masked, active-controlled Treatment duration 64 weeks	**Primary:** To determine if treatment with HD aflibercept Q8 provides non-inferior BCVA change compared to aflibercept 2 mg Q4 **Secondary:** • To determine if treatment with HD aflibercept Q8 requires less injections compared to aflibercept 2 mg Q4 • To determine the effect of HD aflibercept Q8 compared to aflibercept 2 mg Q4 on other visual and anatomic measures of response • To assess the efficacy of HD aflibercept Q8 compared to aflibercept 2 mg Q4 on vision-related QOL • To evaluate the safety of HD aflibercept Q8 compared to aflibercept 2 mg Q4 • To evaluate the PK of HD aflibercept Q8 compared to aflibercept 2 mg Q4	Aflibercept IVT: • 8q8/3: HD aflibercept 8 mg administered Q8 after 3 initial monthly injections • 8q8/5: HD aflibercept 8 mg administered Q8 after 5 initial monthly injections • Aflibercept 2 mg Q4 Prespecified interval adjustments were permitted in the HD groups based on protocol-defined visual and anatomic criteria, with shortening to Q4 allowed from Week 16 (for the 8 mg/3 group) or Week 24 (for the 8 mg/5 group) or lengthening allowed from Week 32 (for the 8 mg/3 group) or Week 40 (for the 8 mg/5 group).	Safety, efficacy, and PK data through Week 36

PULSAR (nAMD): This completed pivotal Phase 3 study provides efficacy data up to Week 96 in participants with nAMD, and up to Week 156 in a subset of participants enrolled in the optional extension phase. The efficacy data through Week 48 are presented for participants who, after receiving three initial monthly doses, either remained on their assigned treatment interval (Q12 or Q16) or had their regimen shortened to Q8 based on visual and anatomic DRM criteria—the minimum dosing interval allowed by the protocol. Additionally, an analysis was conducted on participants who met DRM criteria, had their regimen shortened to Q8, and continued to meet those criteria thereafter.

Table 73: Summary of clinical studies supporting this application (PULSAR)

Study number Report location Study status	Study population	Study design Treatment duration	Study objectives	Treatment, dose, and regimen	Data supporting this application
Neovascular age-related macular degeneration					
Study 20968 (PULSAR) Module 5.3.5.1 PULSAR W48 CSR PULSAR W60 CSR Completed (completion date: LPLV: 07 AUG 2024)	Men or women ≥50 years of age with active subfoveal CNV secondary to nAMD	Phase 3, multicenter, **Main study:** randomized (1:1:1), double-masked, active-controlled Treatment duration: 96 weeks for end of study plus 60 weeks for optional extension phase (total treatment duration up to 156 weeks)	**Primary:** To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg Q8 in participants with nAMD **Secondary:** • To determine the effect of HD aflibercept vs aflibercept 2 mg on other visual and anatomic measures of response • To assess the efficacy of HD aflibercept compared to aflibercept 2 mg on vision-related quality of life • To evaluate the safety of aflibercept • To evaluate the PK and immunogenicity of aflibercept	Aflibercept IVT: • 2q8: aflibercept 2 mg administered Q8 after 3 initial monthly injections • HDq12: HD aflibercept 8 mg administered every 12 weeks after 3 initial monthly injections • HDq16: HD aflibercept 8 mg administered every 16 weeks after 3 initial monthly injections Prespecified interval adjustments were permitted in the HD groups based on protocol-defined visual and anatomic criteria beginning at Week 16 for shortening of intervals (minimum of 8 weeks) and beginning at Week 52 for extending intervals (up to 24 weeks) Optional extension phase: HD aflibercept	Safety, efficacy, and PK data through Week 60

PHOTON (DME): This completed pivotal Phase 2/3 study provides efficacy data up to Week 96 in participants with DME, and up to Week 156 in a subset of participants enrolled in the optional extension phase. The efficacy data through Week 48 are presented for participants who, after receiving three initial monthly doses, either remained on their assigned treatment interval (Q12 or Q16) or had their regimen shortened to Q8 based on visual and anatomic DRM criteria—the minimum dosing interval permitted by the protocol. Additionally, an analysis was conducted on participants who met DRM criteria, were switched to Q8 dosing, and continued to meet those criteria over time.

Table 74: Summary of clinical studies supporting this application (PHOTON)

Study number Report location Study status	Study population	Study design Treatment duration	Study objectives	Treatment, dose, and regimen	Data supporting this application
Diabetic macular edema					
Study 21091 (PHOTON) Module 5.3.5.1 PHOTON W48 CSR PHOTON W60 CSR Completed (completion date: LPLV: 18 JUN 2024)	Men or women ≥18 years of age with type 1 or type 2 diabetes mellitus and center-involved DME	Phase 2/3, multicenter, randomized (1:2:1), double-masked, active-controlled Treatment duration in main study: 96 weeks for end of study plus 60 weeks for optional extension phase (total treatment duration up to 156 weeks)	**Primary:** To determine if treatment with HD aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to aflibercept 2 mg dosed Q8 **Secondary:** • To determine the effect of HD aflibercept vs aflibercept 2 mg on anatomic and other visual measures of response • To evaluate the safety, immunogenicity, and PK of aflibercept	Aflibercept IVT: • 2q8: aflibercept 2 mg administered Q8 after 5 initial monthly injections • HDq12: HD aflibercept 8 mg administered every 12 weeks after 3 initial monthly injections • HDq16: HD aflibercept 8 mg administered every 16 weeks after 3 initial monthly injections Prespecified interval adjustments were permitted in the HD group based on protocol-defined visual and anatomic criteria beginning at Week 16 for shortening of intervals (minimum of 8 weeks) and beginning at Week 52 for extending intervals (up to 24 weeks) Optional extension phase: HD aflibercept	Safety, efficacy, and PK data through Week 60

BCVA=Best corrected visual acuity; CNV=Choroidal neovascularization; CSR=Clinical study report; DBL=Database lock; DME=Diabetic macular edema; HD=High dose; HDq12=Aflibercept 8 mg administered every 12 weeks; HDq16=Aflibercept 8 mg administered every 16 weeks; IAI=Intravitreal aflibercept injection; IVT=Intravitreal; nAMD=Neovascular age-related macular degeneration; PK =pharmacokinetics Q4=every 4 weeks; Q8=every 8 weeks; SAF=Safety analysis set; 2q8=Aflibercept 2 mg administered every 8 weeks
See Definition of Terms for treatment arms description.

CANDELA (nAMD): This completed Phase 2 study provided supportive data through Week 44 for the nAMD indication. Only data related to Q4 dosing exposure are presented.

Table 75: Summary of clinical studies supporting this application (CANDELA)

Study number Report location Study status	Study population	Study design Treatment duration	Study objectives	Treatment, dose, and regimen	Data supporting this application
VGFTe (HD)-AMD-1905 (CANDELA) Study 21086 Module 5.3.5.1 CANDELA CSR Completed (completion date: 30 NOV 2021)	Men or women ≥50 years of age with active subfoveal CNV secondary to nAMD	Phase 2, multicenter, randomized, single-masked, active-controlled Treatment duration 44 weeks	**Primary:** • To determine the safety of HD aflibercept • To determine if HD aflibercept provides greater intraocular pharmacodynamic effect and/or longer duration of action compared to aflibercept 2 mg **Secondary:** There were no secondary objectives in this study	Aflibercept IVT: • IAI 2 mg: aflibercept 2 mg administered monthly as 3 initial Q4 injections (baseline, Week 4, and Week 8), followed by additional doses at Week 20 and Week 32 • HD: HD aflibercept 8 mg administered monthly for 3 initial Q4 injections (baseline, Week 4, and Week 8), followed by additional doses at Week 20 and Week 32 Additional treatment could be given, as frequently as Q4, at weeks 16, 24, 28, 36, and 40 if participants met prespecified criteria	Safety and PK data through Week 44

Q4 Exposure (QUASAR)

○ Macular edema following retinal vein occlusion (QUASAR)

○ *Study population*

All participants began with monthly dosing regimens, receiving 3 to 5 initial monthly injections. Following this initial phase, participants in the high-dose (HD) group had their dosing interval extended to every 8 weeks. However, to account for potential variability in treatment response, the study permitted shortening of the dosing interval to Q4 starting at Week 16 for the 8q8/3 group and at Week 24 for the 8q8/5 group, in participants who met protocol-defined DRM criteria based on a loss of the visual and anatomic improvements achieved during the initial monthly dosing phase.

Table 76: Proportion of participants in the QUASAR Study treated with HD aflibercept who maintained a Q8 interval through week 36 versus those whose interval was shortened from Q8 to Q4 (SAF Completing week 36)

	8q8/3 (N=278)	8q8/5 (N=273)
Maintained Q8 interval, n (%)[1]	246 (88.5%)	255 (93.4%)
Interval shortened from Q8 to Q4[2]	32 (11.5%)	18 (6.6%)

Q4=Every 4 weeks; Q8=Every 8 weeks; n=Number of participants; N=Total number of participants; SAF=Safety analysis set
[1] Maintained Q8 interval includes all participants randomized to 8q8/3 or 8q8/5 who received ≥1 Q8 injection and whose interval was not shortened to a Q4 interval anytime through Week 36.
[2] Interval shortened from Q8 to Q4 includes all participants randomized to 8q8/3 or 8q8/5 who received ≥1 Q8 injection and whose interval was shortened to Q4 anytime through Week 36.
See Definition of Terms for explanation of treatment groups.

Table 77: Demographics and baseline characteristics in participants in the QUASAR Study treated with HD Aflibercept who maintained a Q8 Interval versus those whose Interval was shortened from Q8 to Q4 (FAS Completing week 36)

	Maintained Q8 interval[1]		*Interval shortened from Q8 to Q4[2]*	
	8q8/3 (N=246)	8q8/5 (N=255)	8q8/3 (N=32)	8q8/5 (N=18)
Age at enrollment (years)				
n	246	255	32	18
Mean (SD)	66.2 (11.3)	65.5 (11.2)	65.3 (13.1)	64.1 (11.1)
Median	68.0	66.0	64.5	65.0
Min, Max	23, 95	40, 92	42, 88	42, 82
Race, n (%)				
American Indian or Alaska Native	0	2 (0.8%)	0	0
Asian	85 (34.6%)	87 (34.1%)	4 (12.5%)	3 (16.7%)
Black or African American	6 (2.4%)	8 (3.1%)	1 (3.1%)	0
Native Hawaiian or Other Pacific Islander	0	1 (0.4%)	0	0
White	139 (56.5%)	148 (58.0%)	25 (78.1%)	15 (83.3%)
Multiple	0	1 (0.4%)	0	0
Not Reported	16 (6.5%)	8 (3.1%)	2 (6.3%)	0
Sex, n (%)				
Female	116 (47.2%)	123 (48.2%)	14 (43.8%)	9 (50.0%)
Male	130 (52.8%)	132 (51.8%)	18 (56.3%)	9 (50.0%)
Retinal vein occlusion type, n (%) [3]				
Branch retinal vein occlusion	132 (53.7%)	142 (55.7%)	17 (53.1%)	7 (38.9%)
Central retinal vein occlusion	84 (34.1%)	80 (31.4%)	11 (34.4%)	9 (50.0%)
Hemi-retinal vein occlusion	30 (12.2%)	33 (12.9%)	4 (12.5%)	2 (11.1%)
BCVA (ETDRS letters score)				
n	246	255	32	18
Mean (SD)	55.1 (13.6)	55.9 (13.2)	58.4 (12.2)	50.6 (14.6)
Median	57.0	58.0	60.0	54.5
Min, Max	24, 73	18, 74	24, 73	25, 73
CST (µm)				
n	246	255	32	18
Mean (SD)	622.6 (233.6)	603.4 (217.2)	631.1 (186.1)	656.9 (183.1)
Median	572.0	556.0	593.5	633.5
Min, Max	287, 1499	268, 1424	272, 991	355, 1025

BCVA=Best corrected visual acuity; CST=Central subfield thickness; ETDRS=Early treatment diabetic retinopathy study; FAS=Full analysis set; n=Number of participants; N=Total number of participants; Q4=Every 4 weeks; Q8=Every 8 weeks; SD=Standard deviation
See Definition of Terms for explanation of treatment groups.
[1] Maintained Q8 interval includes all participants randomized to 8q8/3 or 8q8/5 who received ≥1 Q8 injection and whose dosing interval was not shortened to a Q4 interval anytime through Week 36.
[2] Interval shortened from Q8 to Q4 includes all participants randomized to 8q8/3 or 8q8/5 who received ≥1 Q8 injection and whose dosing interval was shortened to Q4 anytime through Week 36.
[3] RVO type based on reading center assessment.

The most common type of RVO among participants enrolled in the study was BRVO, followed by CRVO and then HRVO. Baseline mean BCVA values ranged from 50.6 to 58.4 letters, while mean CST values ranged from 603.4 to 656.9 µm. In the 8q8/3 group, participants whose dosing interval was shortened to Q4 had baseline visual acuity similar to those who did not meet the criteria for interval reduction. In contrast, within the 8q8/5 group, those whose interval was shortened to Q4 had worse baseline visual

acuity compared to participants who maintained the Q8 interval. Across both the 8q8/3 and 8q8/5 groups, participants who met the visual and anatomic DRM criteria for interval shortening to Q4 had thicker retinas at baseline compared to those who remained on the Q8 dosing schedule.

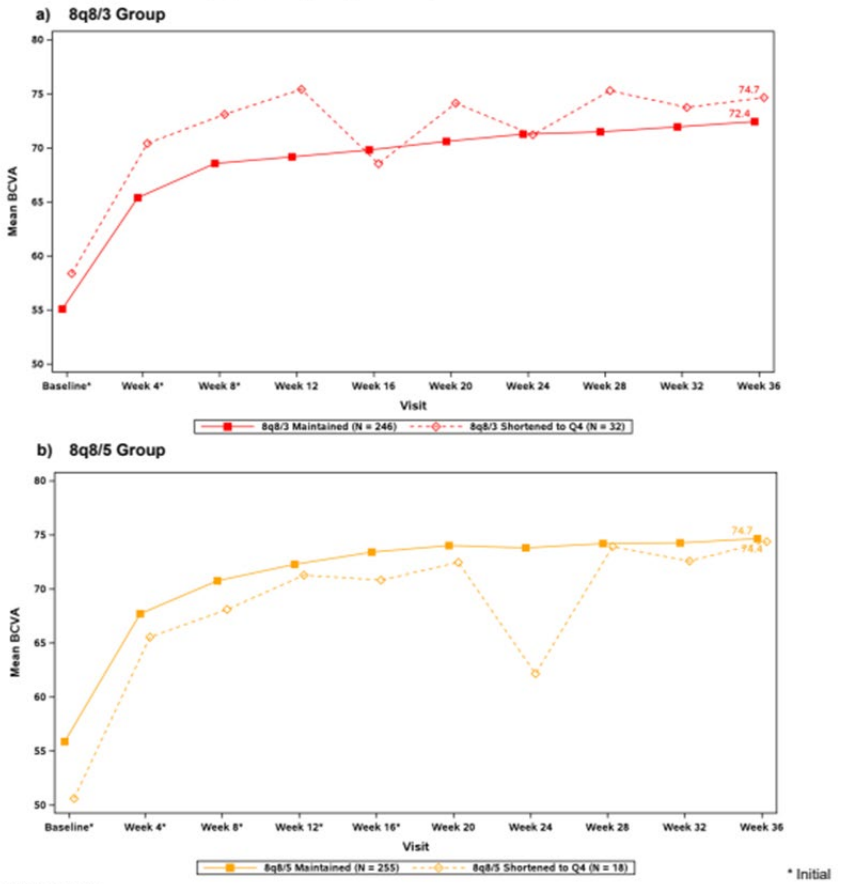
According to Table 72, the majority of participants were able to maintain a Q8 interval. Notably, the 8q8/5 group had a slightly higher proportion of participants maintaining the Q8 interval, with 93.4% (255 participants), compared to 88.5% (246 participants) in the 8q8/3 group. Additionally, a greater number of participants in the 8q8/3 group experienced a shortening of the interval from Q8 to Q4, with 11.5% (32 participants) affected, compared to only 6.6% (18 participants) in the 8q8/5 group.

According to the Table 73, Imbalances in demographic and baseline characteristics were noted between participants who experienced a dosing interval reduction from Q8 to Q4 and those who remained on a Q8 schedule.

- ***Participants who maintained a Q8 interval versus those whose dosing interval was shortened from Q8 to Q4***

    - **BCVA: Mean values and mean change from baseline**

Figure 14 presents the mean BCVA values, and Figure 15 illustrates the mean change in BCVA through Week 36 in the QUASAR study. These figures compare subgroups of participants randomized to the 8q8/3 and 8q8/5 arms who either maintained a Q8 dosing interval or met DRM criteria—based on a loss of initial visual and anatomic gains—and subsequently had their dosing interval shortened from Q8 to Q4 during the same period.



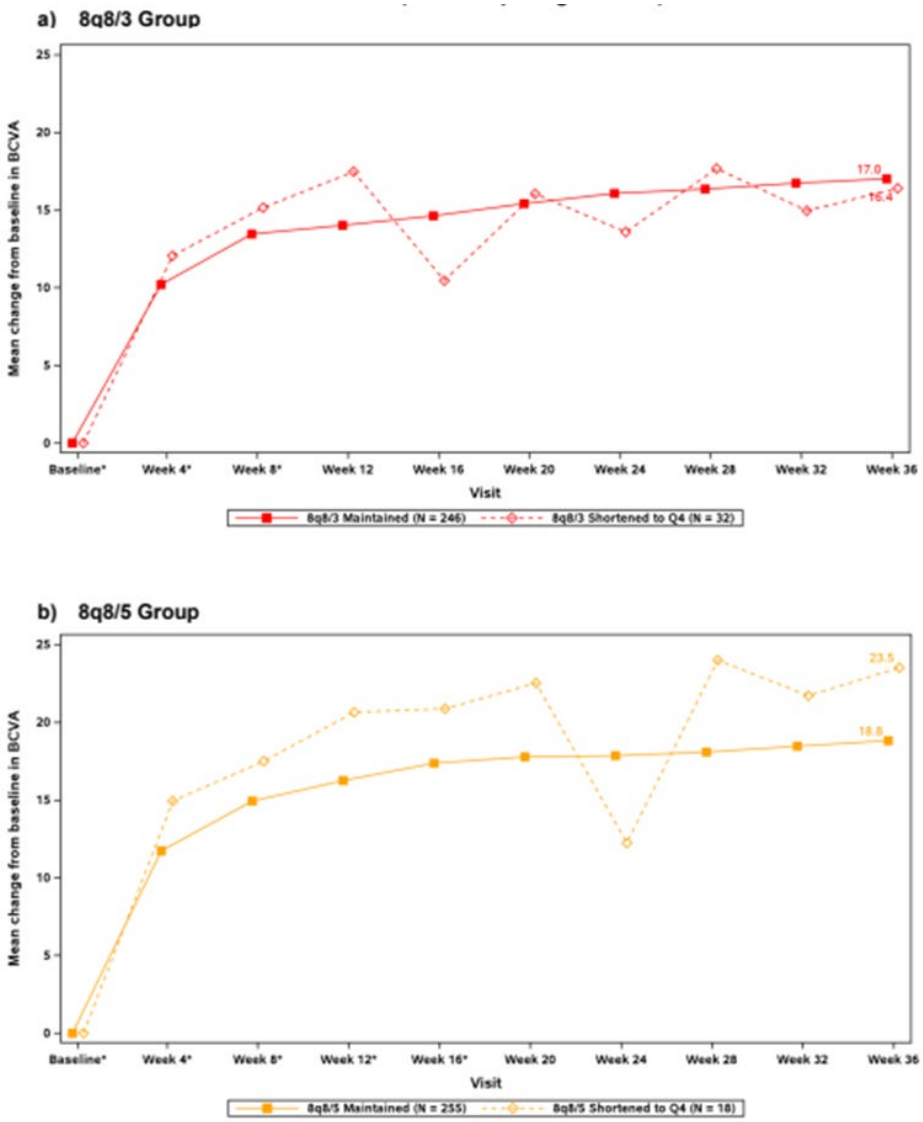
* Initial monthly doses.

Note: In the 8q8/3 group, 32 participants had their interval shortened to Q4; they received their first Q4 dose at Week 16 (n=17), Week 24 (n=10), or Week 32 (n=5), and remained on Q4 through Week 36. In the 8q8/5 group, 18 participants had their interval shortened to Q4; they received their first Q4 dose at Week 24 (n=13), or Week 32 (n=5), and remained on Q4 through Week 36.

BCVA=best corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; FAS=full analysis set; ICE=intercurrent event; N=total number of participants; OC=observed case; Q4=every 4 weeks; Q8=every 8 weeks; SAP=statistical analysis plan

8q8/3 maintained and 8q8/5 maintained includes all participants randomized to 8q8/3 or 8q8/5 who received ≥1 Q8 injection and whose dosing interval was not shortened to a Q4 interval anytime through Week 36. 8q8/3 shortened to Q4 and 8q8/5 shortened to Q4 includes all participants randomized to 8q8/3 or 8q8/5 who received ≥1 Q8 injection and whose dosing interval was shortened to Q4 anytime through Week 36.

Figure 14: Mean BCVA (ETDRS Letters) by visit through week 36 in the 8q8/3 (a) and 8q8/5 (b) groups in participants in the QUASAR study who maintained a Q8 Interval versus those whose Interval was shortened to Q4 (FAS Completing week 36)



* Initial monthly doses.

Note: In the 8q8/3 group, 32 participants had their interval shortened to Q4; they received their first Q4 dose at Week 16 (n=17), Week 24 (n=10), or Week 32 (n=5), and remained on Q4 through Week 36. In the 8q8/5 group, 18 participants had their interval shortened to Q4; they received their first Q4 dose at Week 24 (n=13), or Week 32 (n=5), and remained on Q4 through Week 36.
BCVA=Best corrected visual acuity; ETDRS=Early treatment diabetic retinopathy study; FAS=Full analysis set; ICE=Intercurrent

Figure 15: Mean change in BCVA (ETDRS Letters) by visit through week 36 in the 8q8/3 (a) and 8q8/5 (b) groups in participants in the QUASAR Study who maintained a Q8 interval versus those whose interval was shortened to Q4 (FAS Completing week 36)

Participants in the HD aflibercept groups received three initial monthly injections in the 8q8/3 group and five in the 8q8/5 group before attempting to transition to Q8 dosing. Beginning at Week 16 for the 8q8/3 group and Week 24 for the 8q8/5 group, and at each subsequent Q8 dosing visit, participants were assessed to determine whether they met predefined visual and anatomic DRM criteria for reducing their dosing interval to Q4.

According to Figure 14a, it is observed that the mean BCVA decreases at Week 16 in the subgroups of participants whose interval was shortened from Q8 to Q4. Moreover, the mean baseline vision appears to be similar to that of the Q8/3 maintained group. After Week 16, the mean BCVA also tends to be similar to that of the Q8/3 maintained group

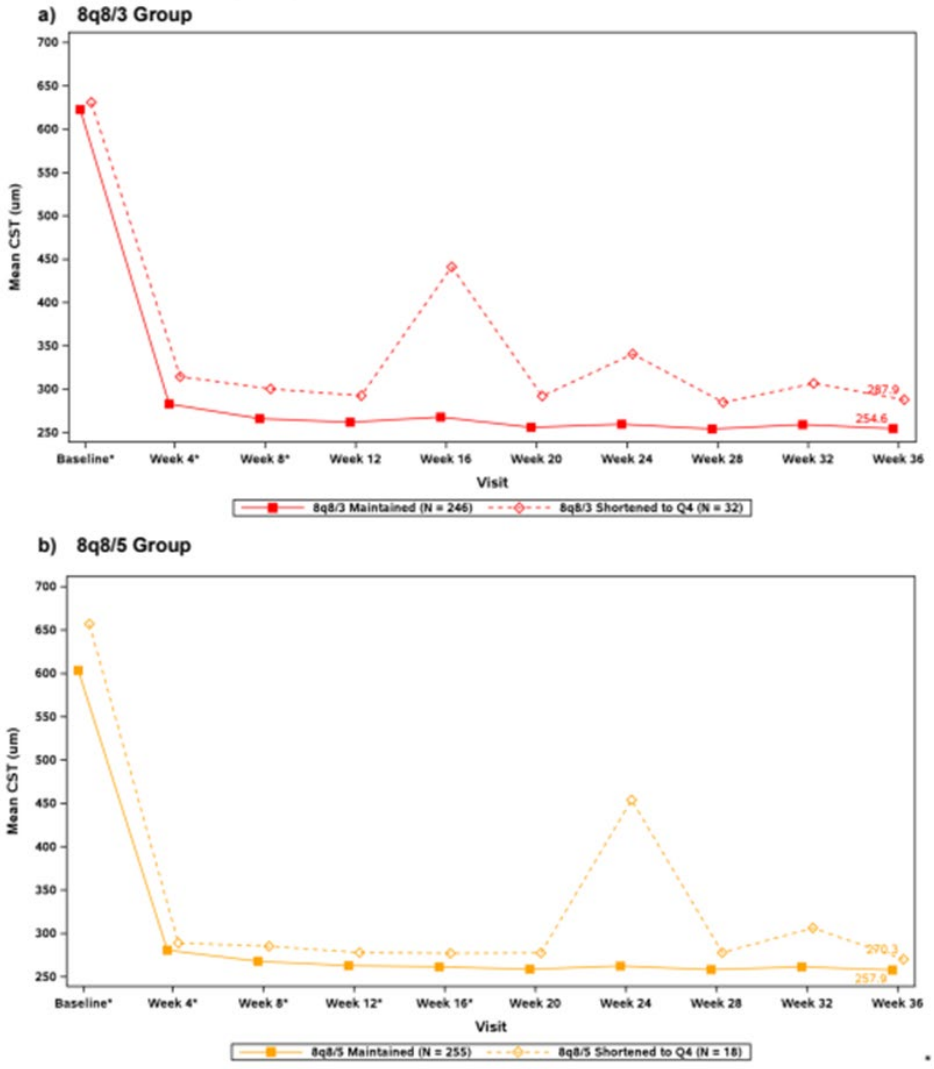
Concerning the 8q8/5 shortened to Q4 (Figure 14b), the difference concerning the mean BCVA is more pronounce at Week 24 comparing to 8q8/5 maintained. After Week 24, Visual outcomes in the Q4 subgroup were similar to those in the Q8 dosing group.

With reference to Figures 15a and 15b, a decline in the mean change from baseline in BCVA is observed at Week 16 for the 8q8/3 subgroup and at Week 24 for the 8q8/5 subgroup, both of which had their dosing interval reduced to Q4. Following these time points, the curves demonstrate an upward trend, indicating a subsequent improvement in visual acuity. These findings therefore suggest a potential visual benefit for patients within the Q4 subgroup.

- **CST: Mean values and mean change from baseline**

Figure 16 displays the mean CST values, and Figure 17 presents the mean change in CST through Week 36 in the QUASAR study. These data compare subgroups of participants randomized to the 8q8/3 and 8q8/5 groups who either maintained a Q8 dosing interval or met DRM criteria—based on a loss of initial visual and anatomic gains—and subsequently had their dosing interval shortened from Q8 to Q4 during the same period.

Figure 16: Mean CST (um) by visit through week 36 in the 8q8/3 (a) and 8q8/5 (b) groups in participants in the QUASAR study who maintained a Q8 Interval versus those whose Interval was shortened to Q4 (FAS Completing week 36)

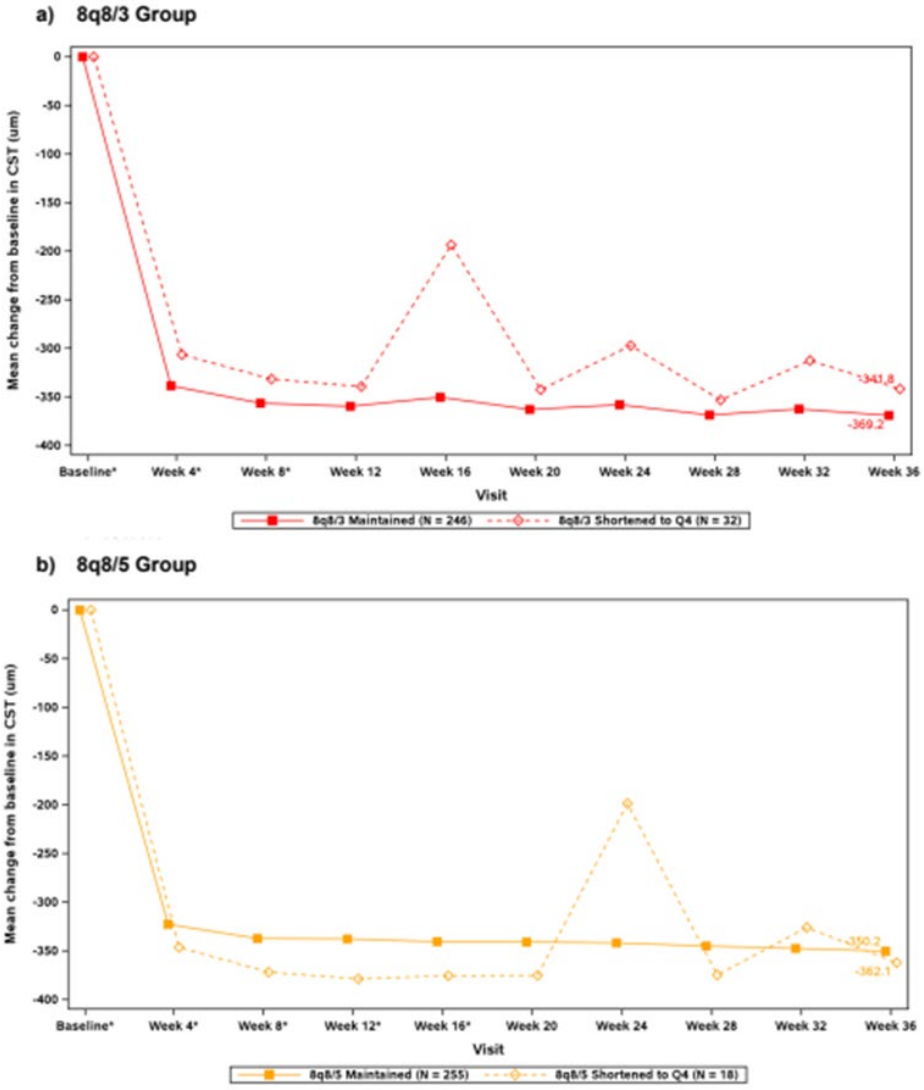


* Initial monthly doses.

Note: In the 8q8/3 group, 32 participants had their interval shortened to Q4; they received their first Q4 dose at Week 16 (n=17), Week 24 (n=10), or Week 32 (n=5), and remained on Q4 through Week 36. In the 8q8/5 group, 18 participants had their interval shortened to Q4; they received their first Q4 dose at Week 24 (n=13), or Week 32 (n=5), and remained on Q4 through Week 36.
CST=Central subfield thickness; FAS=Full analysis set; ICE=Intercurrent event; N=Total number of participants; Q4=Every 4 weeks; Q8=Every 8 weeks; SAP=Statistical analysis plan

8q8/3 maintained and 8q8/5 maintained includes all participants randomized to 8q8/3 or 8q8/5 who received ≥1 Q8 injection and whose dosing interval was not shortened to a Q4 interval anytime through Week 36. 8q8/3 shortened to Q4 and 8q8/5 shortened to Q4 includes all participants randomized to 8q8/3 or 8q8/5 who received ≥1 Q8 injection and whose dosing interval was shortened to

Figure 17: Mean CST (um) by visit through week 36 in the 8q8/3 (a) and 8q8/5 (b) groups in participants in the QUASAR study who maintained a Q8 Interval versus those whose Interval was shortened to Q4 (FAS Completing week 36)



* Initial monthly doses.

Note: In the 8q8/3 group, 32 participants had their interval shortened to Q4; they received their first Q4 dose at Week 16 (n=17), Week 24 (n=10), or Week 32 (n=5), and remained on Q4 through Week 36. In the 8q8/5 group, 18 participants had their interval shortened to Q4; they received their first Q4 dose at Week 24 (n=13), or Week 32 (n=5), and remained on Q4 through Week 36.

CST=Central subfield thickness; FAS=Full analysis set; ICE=Intercurrent events; N=Total number of participants; Q4=Every 4 weeks; Q8=Every 8 weeks; SAP=Statistical analysis plan

8q8/3 maintained and 8q8/5 maintained includes all participants randomized to 8q8/3 or 8q8/5 who received ≥1 Q8 injection and whose dosing interval was not shortened to a Q4 interval anytime through Week 36. 8q8/3 shortened to Q4 and 8q8/5 shortened to Q4 includes all participants randomized to 8q8/3 or 8q8/5 who received ≥1 Q8 injection and whose dosing interval was shortened to Q4 anytime through Week 36.

Observations after an ICE defined for the primary estimand were excluded as described in the SAP.

See Definition of Terms for explanation of treatment groups.

According to the results provided by the Applicant, the Figures 16 and 17 look clearly similar and led to the interpretation that there is an improvement concerning the participants who met DRM criteria with a dosing interval shortened from Q8 to Q4, for the 8q8/3 and 8q8/5 shortened to Q4. Thus, an improvement in mean CST was observed, with Week 36 values returning to levels comparable to those recorded at Week 12 for the 8q8/3 group and at Week 20 for the 8q8/5 group, corresponding to the initial monthly dosing period.

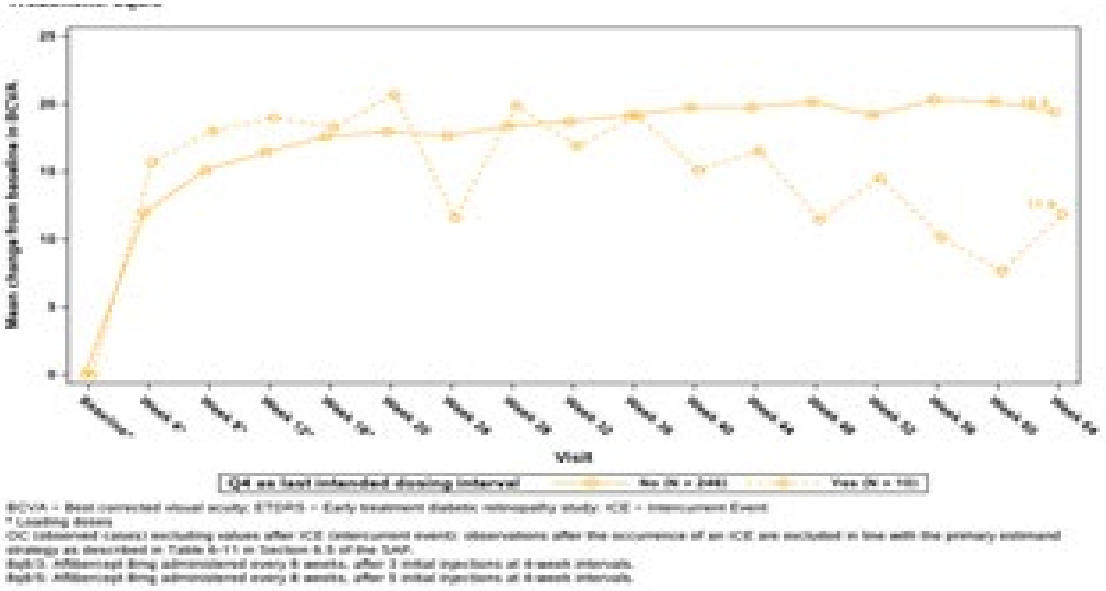
In the QUASAR study, all participants began with monthly dosing regimens, receiving 3 to 5 initial monthly injections. Following this initial phase, participants in the high-dose (HD) group had their dosing interval extended to every 8 weeks. However, to account for potential variability in treatment response, the study permitted shortening of the dosing interval to Q4 starting at Week 16 for the 8q8/3 group and at Week 24 for the 8q8/5 group, in participants who met protocol-defined DRM criteria based on a loss of the visual and anatomic improvements achieved during the initial monthly dosing phase.

Regarding the indication proposed by the Applicant in the product information, and specifically the administration regimen of the 8q8/3 dosage, which provided the longest opportunity to be administered at a Q4 interval, the following information can be highlighted:

The number of patients impacted by this reduction in treatment interval was very low: 32 participants had to be shortened to Q4 at any time out of the 269 who completed the study. Among these 32 patients, 21 could subsequently be extended again to Q8 or beyond for the remainder of the study, and only 11 patients remained on Q4 by Week 64.

If focusing on the results provided by the Applicant concerning the potential efficacy of reducing the injection interval, an efficacy was observed in this small group of patients concerning the 8q8/3 dosage. However, such efficacy was not conclusive for the 8q8/5 dosing regimen, as shown by the difference highlighted in the figure below:

Figure 18: Mean change from baseline in BCVA measured by the ETDRS letter score by visit, OC excluding values after ICE (full analyses set, only participants considered as completers for week 64) (cont.)



At Week 64, the mean change from baseline in BCVA measured by ETDRS letter score for patients in the 8Q8/5 dosage arm showed a marked difference depending on the last intended dosing interval.

Patients without Q4 as last intended dosing interval (N=246) had a mean change of +19.4 letters.

Patients with Q4 as last intended dosing interval (N=10) had a mean change of +11.9 letters.

In contrast to the 8Q8/3 regimen, the 8Q8/5 regimen shows a notable difference between patients depending on their last intended dosing interval. This observation may be explained by the fact that, in the QUASAR study, interval shortening was only permitted from Week 24 onwards, whereas it was

allowed from Week 16 for the 8Q8/3 regimen. Therefore, it cannot be assumed that the results at Week 64 are equivalent between the 8Q8/3 and 8Q8/5 regimens.

The arguments put forward by the Applicant are acceptable with regard to the fact that treatment intensification with aflibercept 8 mg, before considering a switch to another anti-VEGF agent, is a reasonable clinical strategy if clinical outcomes are not satisfactory.

The submitted studies indicate that only a small subgroup requires a 4-week treatment interval; however, QUASAR results suggest that these patients may benefit clinically from such an adjustment.

Q4 Exposure (PULSAR)

Neovascular age-related macular degeneration (PULSAR)

Study population

All participants began with an initial monthly dosing phase consisting of three injections administered at Q4 intervals. Following this phase, participants receiving high-dose (HD) aflibercept had their dosing interval extended to match their assigned regimen (i.e., HDq12 or HDq16), while those receiving aflibercept 2 mg transitioned to a Q8 interval.

To account for potential variability in response to HD aflibercept, the protocol allowed for dosing interval adjustments in 4-week increments in participants who met predefined DRM criteria for interval shortening, based on a loss of the visual and anatomic improvements achieved during the initial monthly dosing phase. The minimum dosing interval permitted per protocol was Q8.

While the majority of participants treated with HD aflibercept maintained their randomized dosing interval, a subset of participants experienced a loss of initial visual gains which based on the DRM criteria resulted in a shortening of their dosing interval from Q12 or Q16 to Q8.

Table 78: Proportion of participants in the PULSAR Study treated with HD aflibercept who maintained their randomized interval through Week 48 versus those whose interval was shortened to Q8 after the initial monthly dosing phase (SAF Completing Week 48)

	HDq12 (N=316)	HDq16 (N=312)
Maintained randomized interval, n (%)[1]	251 (79.4%)	239 (76.6%)
Interval shortened at any time[2]	65 (20.6%)	73 (23.4%)
Interval shortened to Q8 at any time[3]	65 (20.6%)	40 (12.8%)[3]

DRM=Dose regimen modification; n=Number of participants; N=Total number of participants; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAF=Safety analysis set

1 Maintained randomized interval includes all participants randomized to HDq12 whose dosing interval was not shortened to Q8 through Week 48, and all participants randomized to HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48.

2 Interval shortened at any time includes all participants randomized to HDq12 who met visual and anatomic DRM criteria and whose interval was shortened from an extended interval to Q8 (after 3 initial monthly doses), and all participants randomized to HDq16 who met visual and anatomic DRM criteria and whose interval was shortened to Q12 or Q8 (after 3 initial monthly doses) anytime through Week 48.

3 Interval shortened to Q8 at any time includes all participants randomized to HDq12 or HDq16 who met visual and anatomic DRM criteria and whose interval was shortened from an extended interval to Q8 (after 3 initial monthly doses) anytime through Week 48. A total of 33 (10.6%) participants in the HDq16 group had their interval shortened to Q12 without shortening to Q8.

See Definition of Terms for explanation of treatment groups.

Table 79: Demographics and baseline characteristics in participants in the PULSAR Study treated with HD aflibercept who maintained their randomized interval versus those whose interval was shortened to Q8 (FAS Completing week 48)

	Maintained on Q12 or Q16[1]		Interval Shortened to Q8[2]	
	HDq12 (N=251)	HDq16 (N=239)	HDq12 (N=65)	HDq16 (N=40)
Age (years)				
n	251	239	65	40
Mean (SD)	74.8 (7.6)	74.4 (8.6)	73.2 (8.8)	75.4 (8.2)
Median	75.0	74.0	74.0	76.0
Min : Max	52, 93	56, 95	54, 92	59, 93
Race, n (%)				
American Indian or Alaska Native	0	0	0	0
Asian	54 (21.5%)	62 (25.9%)	12 (18.5%)	3 (7.5%)
Black or African American	2 (0.8%)	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	192 (76.5%)	177 (74.1%)	53 (81.5%)	37 (92.5%)
Multiple	1 (0.4%)	0	0	0
Not Reported	2 (0.8%)	0	0	0
Sex, n (%)				
Female	140 (55.8%)	132 (55.2%)	34 (52.3%)	20 (50.0%)
Male	111 (44.2%)	107 (44.8%)	31 (47.7%)	20 (50.0%)
BCVA (ETDRS letter score)				
n	251	239	65	40
Mean (SD)	59.4 (13.7)	60.8 (12.0)	61.7 (13.2)	56.2 (14.5)
Median	62.0	63.0	65.0	57.0
Min : Max	25 , 78	24 , 78	24 , 78	26 , 76
CRT (microns)				
n	251	237	65	40
Mean (SD)	371.5 (128.0)	353.3 (127.0)	366.5 (115.3)	446.8 (161.8)
Median	352.0	320.0	344.0	413.0
Min : Max	151, 840	144, 913	153, 793	203, 849

BCVA=Best corrected visual acuity; CRT=Central subfield retinal thickness; ETDRS=Early treatment diabetic retinopathy study; FAS=Full analysis set; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks

[1] Maintained on Q12 or Q16 includes all participants randomized to HDq12 whose dosing interval was not shortened to Q8 through Week 48, and all participants randomized to HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48.

[2] Interval shortened to Q8 includes all participants randomized to HDq12 or HDq16 whose dosing interval was shortened from an assigned Q12 or Q16 regimen to Q8 (after 3 initial monthly doses) anytime through Week 48.

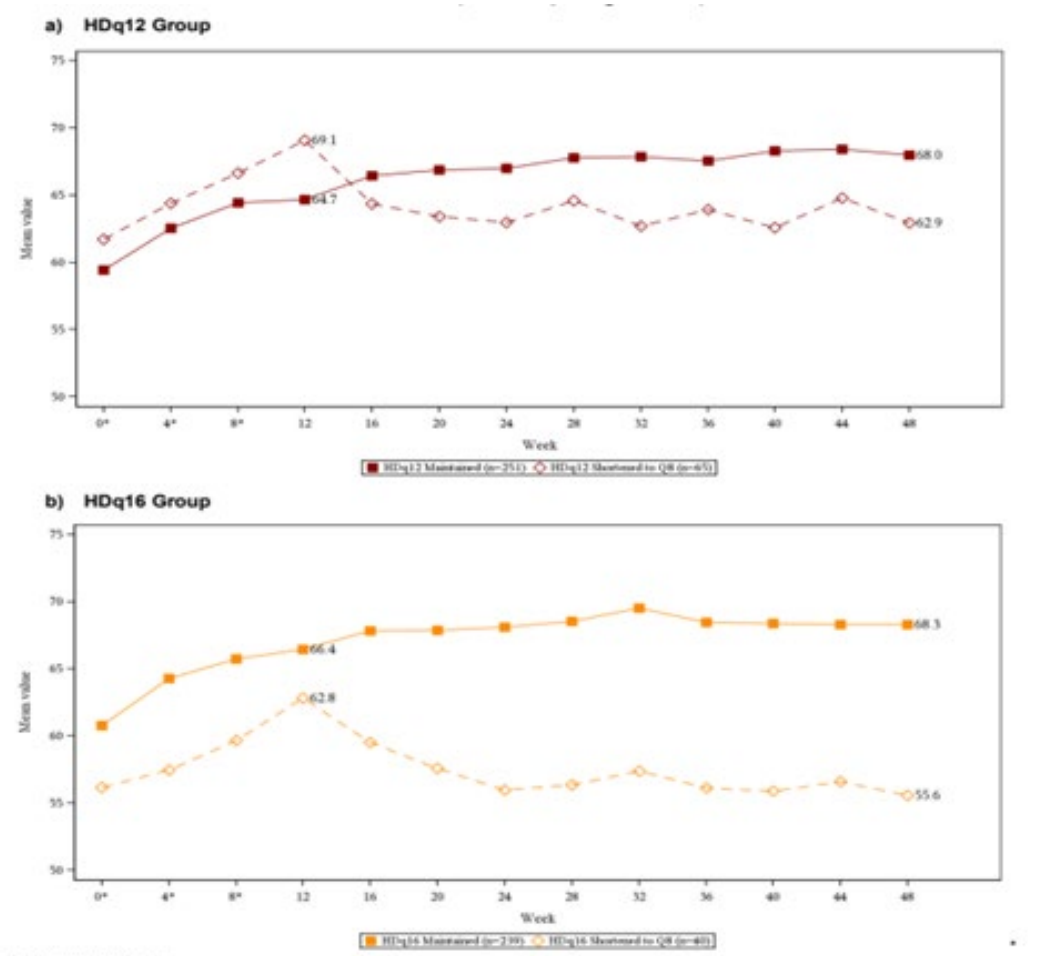
See Definition of Terms for explanation of treatment groups.

The proportion of participants in the PULSAR study appears to be similar across the different subgroups: those who maintained their randomized interval, those whose interval was shortened at any time, and those whose interval was shortened specifically to Q8 at any time. However, it is observed that the subgroup with intervals shortened to Q8 at any time is smaller in the HDq16 group (40 participants, 12.8%) compared to the HDq12 group (65 participants, 20.6%). Concerning the demographics and baseline characteristics in participants in the PULSAR study, differences in demographic and baseline characteristics were noted between the subgroups of participants who had their dosing interval shortened from the originally assigned Q12 or Q16 regimen to Q8, and those who remained on their assigned Q12 or Q16 regimen. Baseline mean BCVA values ranged from 56.2 concerning the HDq16 with interval shortened to Q8 to 61.7 EDTRS letter for the HDq12 with interval shortened to Q8, while mean CRT values ranged from 353.3 concerning the HDq12 with maintained on Q12 to 446.8 µm for HDq16 with interval shortened to Q8.

- ***Participants who maintained their randomized interval versus those whose dosing interval was shortened from an assigned Q12 or Q16 regimen to Q8***

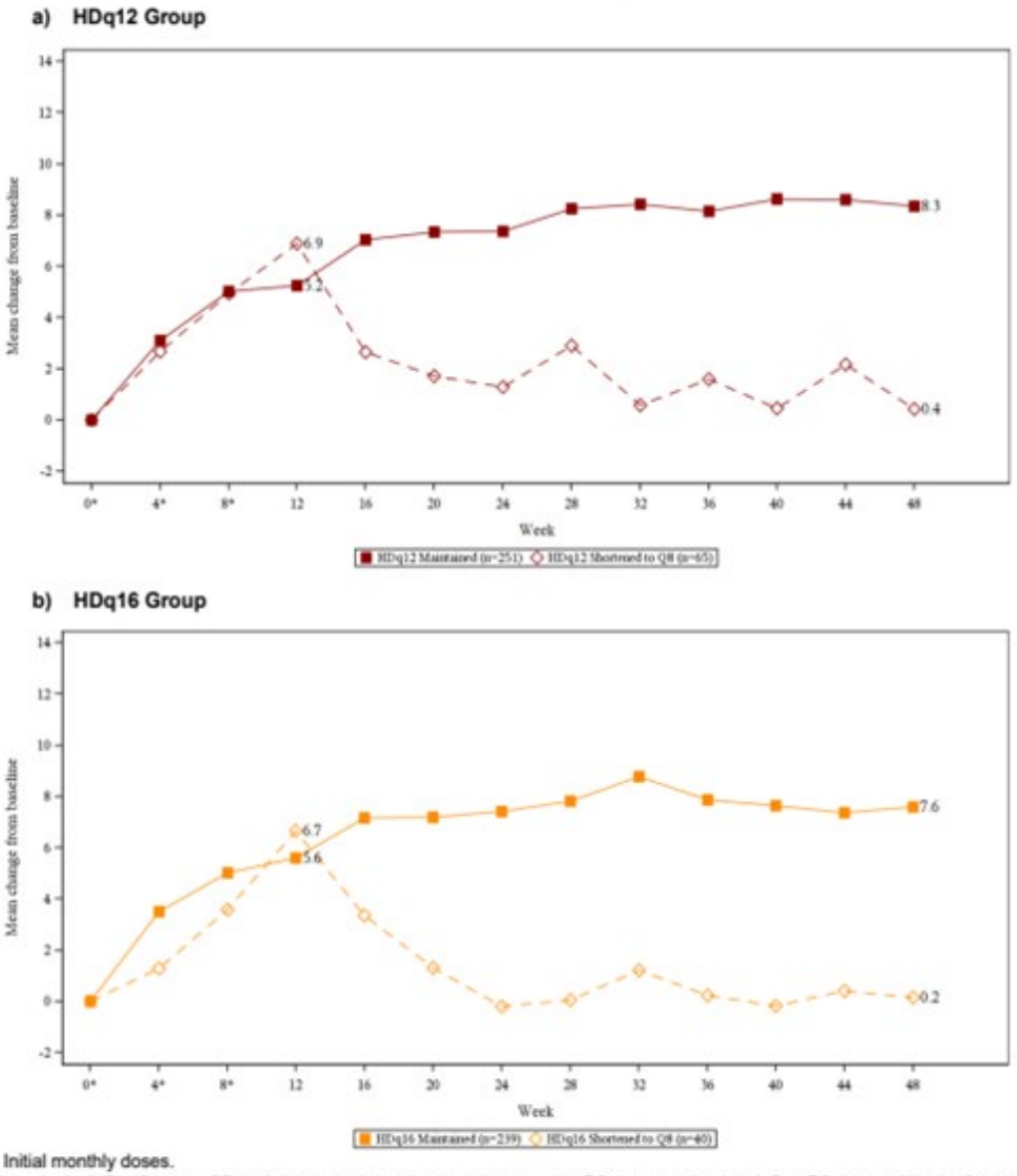
    - **BCVA mean values and mean change from baseline**

Figure 19 presents the mean BCVA values, and Figure 20 shows the mean change from baseline in BCVA through Week 48 in the PULSAR study. These figures compare subgroups of participants randomized to the HDq12 and HDq16 groups who either maintained their assigned Q12 or Q16 dosing interval or met the visual and anatomic DRM criteria for interval shortening and subsequently had their dosing interval reduced to Q8.



Initial monthly doses.
Note: In the HDq12 group, 65 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=17), Week 20 (n=25), or subsequent dosing visits (n=23), and remained on Q8 through Week 48. In the HDq16 group, 40 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=10), Week 20 (n=21), or subsequent dosing visits (n=9), and remained on Q8 through Week 48.
BCVA=Best corrected visual acuity; DRM=Dose regimen modification; FAS=Full analysis set; ICE=Intercurrent event; n=Number of participants; OC=Observed cases; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAP=Statistical analysis plan. HDq12 maintained and HDq16 maintained includes all participants randomized to HDq12 or HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48. HDq12 shortened to Q8 and HDq16 shortened to Q8 includes all participants randomized

Figure 19: Mean BCVA (ETDRS Letters) by visit through Week 48 in the HDq12 (a) and HDq16 (b) groups in participants in the PULSAR study who maintained a Q12 or Q16 dosing interval versus those whose interval was shortened to Q8 (FAS Completing week 48)



* Initial monthly doses.

Note: In the HDq12 group, 65 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=17), Week 20 (n=25), or subsequent dosing visits (n=23), and remained on Q8 through Week 48. In the HDq16 group, 40 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=10), Week 20 (n=21), or subsequent dosing visits (n=9), and remained on Q8 through Week 48.

BCVA=Best corrected visual acuity; DRM=Dose regimen modification; FAS=Full analysis set; ICE=Intercurrent event; n=Number of participants; OC=Observed cases; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAP=Statistical analysis plan.

HDq12 maintained and HDq16 maintained includes all participants randomized to HDq12 or HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48. HDq12 shortened to Q8 and HDq16 shortened to Q8 includes all participants randomized to HDq12 or HDq16 who met visual and anatomic DRM criteria and whose dosing interval was shortened from an extended interval to Q8 (after 3 initial monthly doses) anytime through Week 48.

Observations after an ICE defined for the primary estimand were excluded as described in the SAP.

See Definition of Terms for explanation of treatment groups.

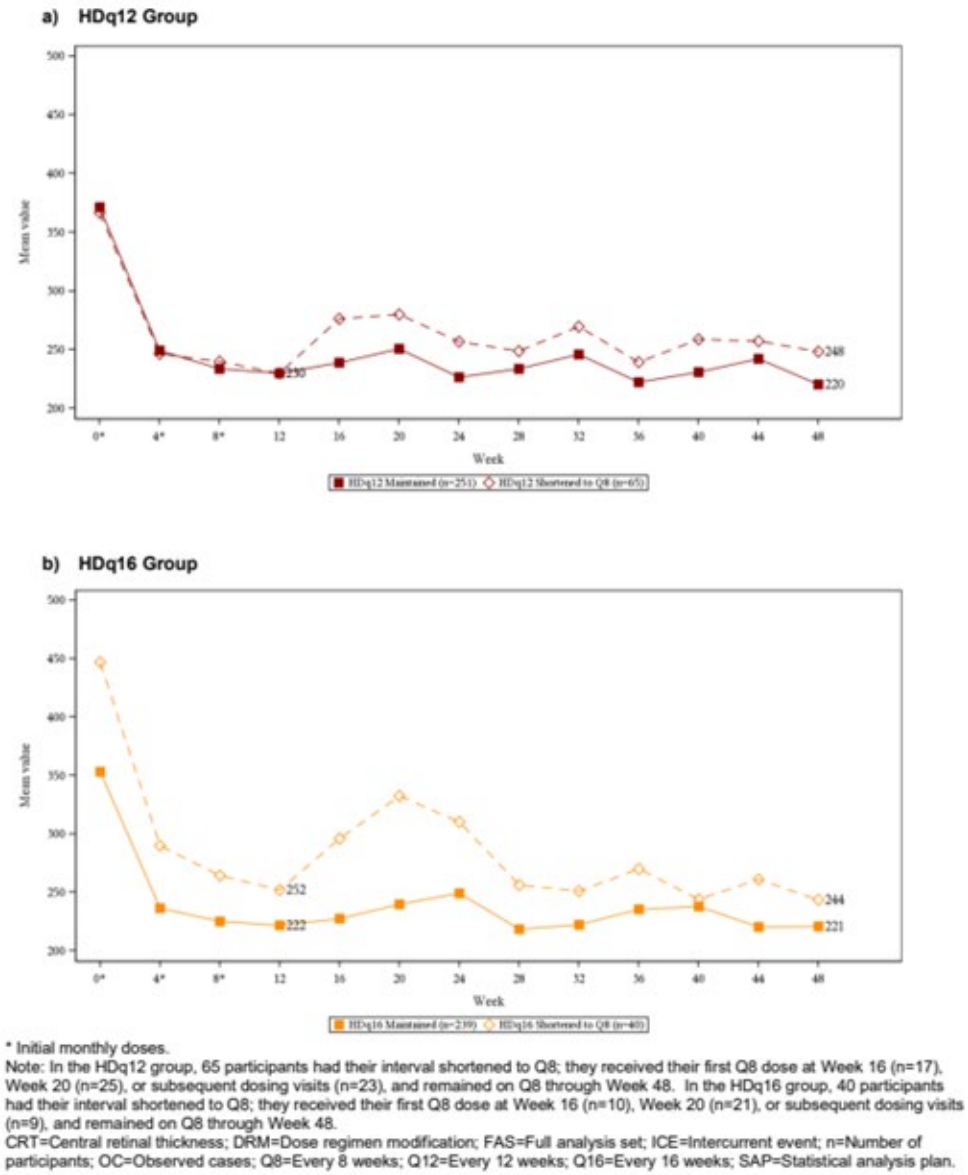
Figure 20: Mean change in BCVA (ETDRS Letters) by visit through week 48 in the HDq12 (a) and HDq16 (b) groups in participants in the PULSAR Study who maintained a Q12 or Q16 interval versus those whose interval was shortened to Q8 (FAS Completing week 48)

From Week 16, in both the HDq12 and HDq16 groups, when the time between injections increased and 8 weeks had passed since the last HD aflibercept dose, participants in the HDq12 and HDq16 subgroups who met the criteria to switch to Q8 dosing experienced a decline in mean BCVA and also mean change from baseline. On average, they did not regain the vision improvements they had seen at Week 12.

Consequently, based on these data, the MAH concluded that more frequent dosing of aflibercept 8 mg may be necessary to preserve and/or improve vision in patients with treatment-resistant nAMD.

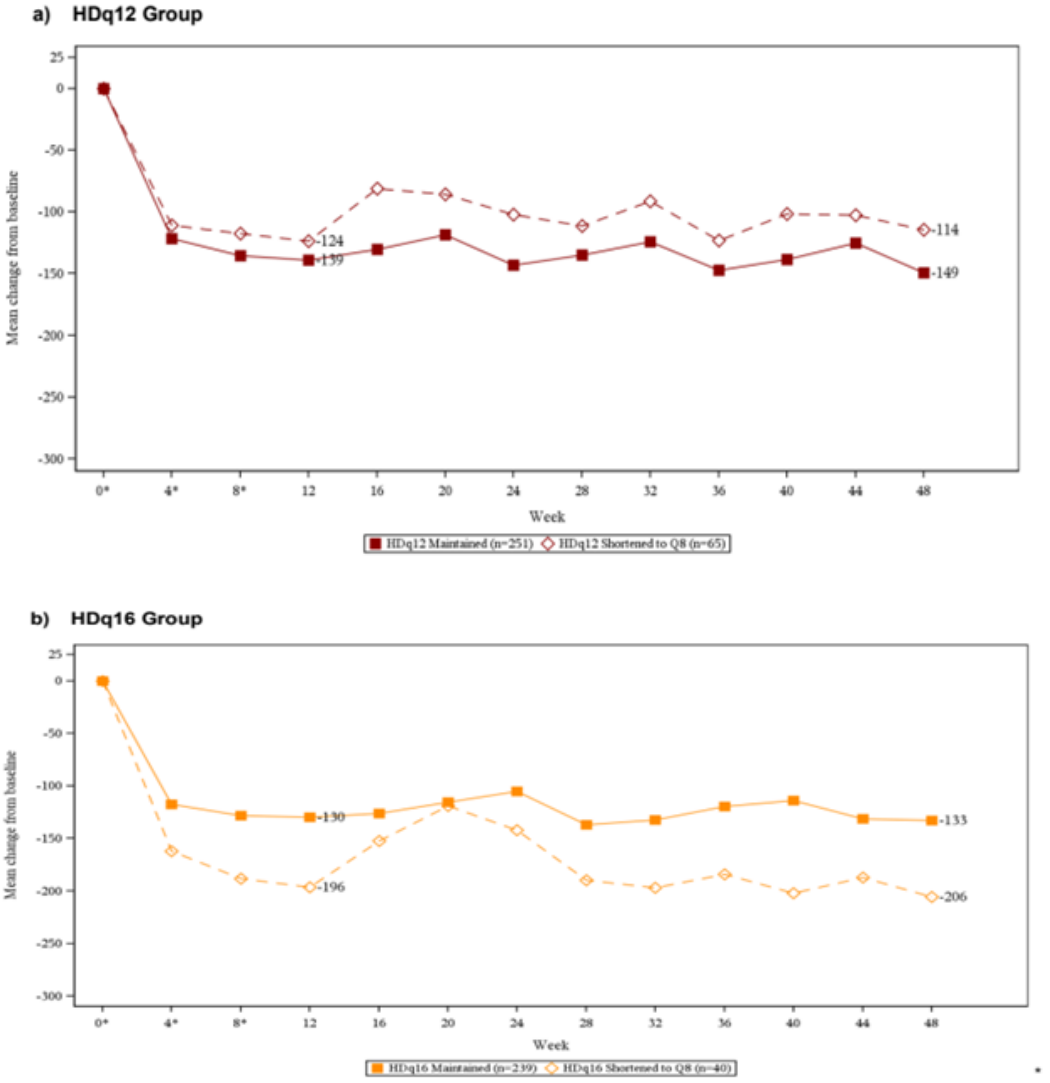
- **CRT: Mean values and mean changes from baseline**

Figure 21 displays the mean CRT values, and Figure 22 presents the mean change from baseline in CRT through Week 48 in the PULSAR study. These figures compare subgroups of participants randomized to the HDq12 and HDq16 groups who either maintained their assigned Q12 or Q16 dosing intervals or met visual and anatomic DRM criteria and subsequently had their interval shortened to Q8.



* Initial monthly doses.
Note: In the HDq12 group, 65 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=17), Week 20 (n=25), or subsequent dosing visits (n=23), and remained on Q8 through Week 48. In the HDq16 group, 40 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=10), Week 20 (n=21), or subsequent dosing visits (n=9), and remained on Q8 through Week 48.
CRT=Central retinal thickness; DRM=Dose regimen modification; FAS=Full analysis set; ICE=Intercurrent event; n=Number of participants; OC=Observed cases; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAP=Statistical analysis plan.

Figure 21: Mean CRT (um) by visit through week 48 in the HDq12 (a) and HDq16 (b) groups in participants in the PULSAR Study who maintained a Q12 or Q16 Interval versus those whose interval was shortened to Q8 (FAS Completing week 48)



Initial monthly doses.
Note: In the HDq12 group, 65 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=17), Week 20 (n=25), or subsequent dosing visits (n=23), and remained on Q8 through Week 48. In the HDq16 group, 40 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=10), Week 20 (n=21), or subsequent dosing visits (n=9), and remained on Q8 through Week 48.
CRT=Central retinal thickness; DRM=Dose regimen modification; FAS=Full analysis set; ICE=Intercurrent event; n=Number of participants; OC=Observed cases; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAP=Statistical analysis plan.
HDq12 maintained and HDq16 maintained includes all participants randomized to HDq12 or HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48. HDq12 shortened to Q8 and HDq16 shortened to Q8 includes all participants randomized to HDq12 or HDq16 who met visual and anatomic DRM criteria and whose dosing interval was shortened from an extended interval to Q8 (after 3 initial monthly doses) anytime through Week 48.
Observations after an ICE defined for the primary estimand were excluded as described in the SAP.
See Definition of Terms for explanation of treatment groups.

Figure 22: Mean change in CRT (um) by visit through Week 48 in the HDq12 (a) and HDq16 (b) groups in participants in the PULSAR study who maintained a Q12 or Q16 interval versus those whose interval was shortened to Q8 (FAS completing week 48)

Regarding the mean values and mean changes from baseline, the difference between Q8 dosing and participants who maintained HDq12 or HDq16 is not clearly demonstrated. The data appear to be similar across the groups. A greater difference in mean change from baseline is observed for the HDq16 group shortened to Q8 compared to the HDq16 group that maintained their dosing interval. However, these results should be interpreted with caution, as the Q8 dosing group had a higher baseline CRT (average around 450 µm) compared to the HDq16 maintained group, which had a baseline CRT of approximately 350 µm.

- ***Participants whose dosing interval was shortened to Q8 who continued to meet DRM criteria for interval shortening***

Table 76: Proportion of participants in the PULSAR Study whose dosing interval was shortened from Q12 or Q16 to Q8 and who continued to meet DRM criteria through week 48 (SAF Completing week 48) highlights participants in the PULSAR study who were treated with either HD aflibercept or aflibercept 2 mg and continued to meet DRM criteria while on the shortest maintenance interval permitted by the protocol (Q8).

Figure 23 presents the mean BCVA values in the All HD group (i.e., participants randomized to either HDq12 or HDq16), categorized into three subgroups: those whose dosing interval had already been shortened to Q8 and who continued to meet both visual and anatomic DRM criteria; those who initially met DRM criteria and had their dosing interval shortened to Q8 but subsequently no longer met the criteria; and those who maintained a Q12 or Q16 dosing interval through Week 48.

Table 80: Proportion of participants in the PULSAR Study whose dosing interval was shortened from Q12 or Q16 to Q8 and who continued to meet DRM criteria through week 48 (SAF Completing week 48)

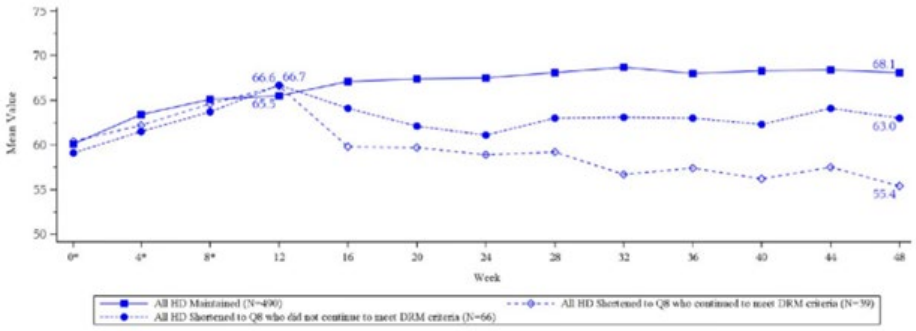
	2q8 (N=309)	HDq12 (N=316)	HDq16 (N=312)	All HD (N=628)
Participants who were shortened to Q8 and continued to meet DRM criteria, n (%)	45 (14.6%)	24 (7.6%)	15 (4.8%)	39 (6.2%)

BCVA=Best corrected visual acuity; CRT=Central retinal thickness; DRM=Dose regimen modification; n=Number of participants N=Total Number of participants; Q4=Every 4 weeks; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAF=Safety analysis set

Derived DRM criteria used the same DRM criteria for shortening the dosing interval to Q8. Percentages of participants who completed Week 48 in the HDq12, HDq16 and 2q8 groups and continued to meet DRM criteria (and would have had the dosing interval shortened to Q4) were based on participants whose dosing interval had already been shortened to Q8 at any time through Week 48 for the HD groups, and for all participants in the 2q8 group. The derived DRM criteria was met if there was a BCVA >5-letter loss from Week 12 AND CRT >25 µm increase from Week 12 at a scheduled dosing visit or if there was new foveal hemorrhage or new foveal neovascularization.

The percentage is based on the number of participants in each treatment group as denominator.

See Definition of Terms for explanation of treatment groups.



* Initial monthly doses.

BCVA=Best corrected visual acuity; CRT=Central retinal thickening; DRM=Dose regimen modification; FAS=Full analysis set; N=Total number of participants; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks

All HD maintained includes all participants in the HDq12 or HDq16 groups whose dosing interval was not shortened to Q8 or Q12 through Week 48. All HD Shortened to Q8 who did not continue to meet DRM criteria includes all participants in the HDq12 or HDq16 groups who met DRM criteria and whose dosing interval was shortened to Q8 but did not continue to meet the derived DRM criteria through Week 48. All HD shortened to Q8 who continued to meet DRM criteria includes all participants in the HDq12 or HDq16 groups who met DRM criteria and whose dosing interval was shortened to Q8 and continued to meet the derived DRM criteria through Week 48.

The derived DRM criteria met if there was a BCVA >5-letter loss from Week 12 AND CRT >25 µm increase from Week 12 at a scheduled dosing visit or if there was new foveal hemorrhage or new foveal neovascularization.

Observations after an ICE defined for the primary estimand were excluded as described in the SAP.

See Definition of Terms for explanation of treatment groups.

Figure 23: Mean BCVA (ETDRS Letters) by visit through week 48 in the All HD Group in the PULSAR Study in participants who maintained a Q12 or Q16 interval, those who met DRM criteria and whose dosing interval was shortened to Q8 but did not continue to meet DRM Criteria, and those whose dosing interval was shortened to Q8 who continued to meet DRM criteria for further interval shortening (FAS Completing week 48)

When comparing Table 76 and Table 74 , which show the proportion of participants in the PULSAR study treated with HD aflibercept who maintained their randomized interval through Week 48 versus those whose interval was shortened to Q8 after the initial monthly dosing phase (SAF Completing Week 48), it is observed that out of 105 participants (HDq12/HDq16 interval shortened to Q8 at any time), 39 (37.1%) continued to meet the DRM criteria.
According to Figure 23, among the participants who met the DRM criteria for shortening to Q8, those who continued to meet these criteria had the lowest mean BCVA outcomes between Week 16 and Week 48.

Q4 dosing for patients with DME and nAMD:

To support a potential efficacy of shortening the treatment interval to 4 weeks, the Applicant relies on three studies: one based on modelling and simulations, and two based on real-world data.

Modelling and simulation:

The conclusions drawn from these simulated trials are that the subset of participants with nAMD or DME who continued to meet DRM criteria after their dosing interval was shortened to Q8 showed further improvements in CST and BCVA when their dosing interval was subsequently reduced to Q4, compared with participants who remained on a Q8 interval.

SPECTRUM

SPECTRUM is a global, prospective, observational study aimed at assessing the real-world effectiveness of intravitreal aflibercept 8 mg in patients with nAMD or DME, either treatment-naïve or previously treated, in routine clinical practice.

Enrolment started on 15 February 2024 was completed by 30 September 2025. Overall, 3739 patients with naïve or previously treated neovascular nAMD or DME were enrolled and are planned to be observed for 24 months.

The focus was on the results corresponding to the Applicant’s variation request, namely a reduction of the injection interval to 4 weeks. Furthermore, in order to align as closely as possible with the studies previously submitted by the Applicant (PHOTON and PULSAR), only treatment-naïve patients were considered.

Naive nAMD and Naïve DME:

The results provided by the Applicant suggest a stabilization of visual acuity as well as of CRT over time in treatment-naïve patients who required intervals shorter than Q8. Equivalent results were observed in patients with DME.

However, it should be noted that these evaluations included patients whose dosing interval was reduced to Q4 as well as to Q6.

To conclude, the latest data provided by the Applicant have proven to be convincing: Further details were requested concerning the data from the SPECTRUM and FRB! studies.

For the SPECTRUM study, the Applicant was asked to provide data highlighting the efficacy of the treatment in treatment-naïve patients who, after the initiation phase, received one or more doses of aflibercept 8 mg at 4-week intervals. Additionally, the results were to be compared with those obtained in the treatment-naïve population who did not require a reduction of the treatment interval to 4 weeks.

Concerning the FRB! Study, the Applicant was requested to provide complementary information, particularly on the reduction of aflibercept 8 mg injection intervals to 4 weeks for patients requiring a

dose adjustment, and to compare the efficacy of these patients with those not requiring a dose adjustment.

To support its argument, the Applicant emphasized that it is more appropriate to compare patients treated with frequent injections and intensive therapy to untreated patients, rather than directly comparing outcomes between patients receiving intensive versus less intensive treatment. Such a direct comparison can be biased, as these are self-selected groups based on their response to treatment. Patients treated more frequently may have more severe disease and/or may be more difficult to treat, while those treated at longer intervals may have a more pronounced response to treatment and therefore achieve a benefit with longer intervals.

SPECTRUM:

SPECTRUM is an ongoing, global, prospective, observational study designed to evaluate the real-world effectiveness of intravitreal aflibercept 8 mg in patients with neovascular age-related macular degeneration (nAMD) or diabetic macular edema (DME). The study includes both treatment-naïve patients and those previously treated, reflecting routine clinical practice.

The study evaluated different dosing interval groups (<8 weeks, 4 weeks, 6 weeks, and ≥8 weeks) and the data reported for these respective groups include:

- Change in visual acuity letters score from baseline to Month 12
- Visual acuity letters score at Month 12
- Change in central retinal thickness (CRT; µm) from baseline to Month 12
- CRT (µm) at Month 12

The data provided by the Applicant support the efficacy of the treatment when the dosing interval is reduced to less than 8 weeks. Indeed, the observed outcomes are equivalent to those seen in patients who did not require a dosing interval of less than 8 weeks, for both patients previously treated or naive with neovascular age-related macular degeneration (nAMD) and those with diabetic macular edema (DME).

It is also agreed that the option to reduce the dosing interval to less than 8 weeks provides an additional treatment choice for patients refractory to the Q8 dosing. This flexibility is valuable, and if the shorter interval does not prove effective, patients can then switch to other therapies.

FRB!

This is an advanced, web-based ophthalmic registry designed to collect and track clinical practice data and outcomes for retinal diseases—including neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME)—across multiple countries. However, the Applicant has submitted results for neovascular age-related macular degeneration (nAMD) only, as the data for diabetic macular edema (DME) are insufficient. Overall, the data provided by the Applicant for this study are limited. The data from this study are not necessarily interpretable due to their limited scope and the fact that they focus solely on one condition (nAMD). However, this study primarily supports the observation that, in routine clinical practice, dose interval shortening is commonly implemented.

In conclusion, regarding the data provided by the Applicant, the results are conclusive in demonstrating a therapeutic benefit for patients who are refractory to longer dosing intervals for patient suffering from nAMD and DME.

Q4 Exposure (PHOTON)

Diabetic macular edema (PHOTON)

Study population

All participants randomized to the HD groups began treatment with an initial monthly dosing phase consisting of 3 injections administered at 4-week (Q4) intervals. Following this initial phase, HD participants had their dosing intervals extended according to their assigned regimen (i.e., HDq12 or HDq16 for HD aflibercept; Q8 for 2 mg aflibercept). However, to account for potential variability in response to HD aflibercept, the study permitted dosing interval adjustments in 4-week increments for participants who met the protocol-defined Disease Reactivation Monitoring (DRM) criteria for interval shortening. These adjustments were based on a loss of the initial visual and anatomical improvements achieved during the initial monthly dosing phase. According to the protocol, the minimum allowed dosing interval was Q8.

Although most participants treated with HD aflibercept maintained their assigned dosing intervals, a subgroup had their intervals shortened from the randomized Q12 or Q16 schedule to Q8 due to meeting the DRM criteria for interval shortening.

Table 81: Proportion of participants in the PHOTON Study treated with HD aflibercept who maintained their randomized interval through week 48 versus those whose interval was shortened to Q8 after the initial monthly dosing phase (SAF Completing week 48)

	HDq12 (N=300)	HDq16 (N=156)
Maintained randomized interval, n (%)[1]	273 (91.0%)	139 (89.1%)
Interval shortened at any time[2]	27 (9.0%)	17 (10.9%)
Interval shortened to Q8 at any time[3]	27 (9.0%)	6 (3.8%)[3]

DRM=Dose regimen modification; N=Total number of participants; n=Number of participants; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAF=Safety analysis set

[1] Maintained randomized interval includes all participants randomized to HDq12 whose dosing interval was not shortened to Q8 through Week 48, and all participants randomized to HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48.

[2] Interval shortened at any time includes all participants randomized to HDq12 who met visual and anatomic DRM criteria and whose interval was shortened from an extended interval to Q8 (after 3 initial monthly doses), and all participants randomized to HDq16 who met visual and anatomic DRM criteria and whose interval was shortened to Q12 or Q8 (after 3 initial monthly doses) anytime through Week 48.

[3] Interval shortened to Q8 at any time includes all participants randomized to HDq12 or HDq16 who met visual and anatomic DRM criteria and whose interval was shortened from an extended interval to Q8 (after 3 initial monthly doses) anytime through Week 48. A total of 11 (7%) participants in the HDq16 group had their interval shortened to Q12 without shortening to Q8.

See Definition of Terms for explanation of treatment groups.

Table 82: Demographics and baseline characteristics in participants in the PHOTON Study treated with HD Aflibercept who Maintained their randomized interval versus those whose interval was shortened to Q8 (FAS Completing week 48)

	Maintained on Q12 or Q16[1]		Interval Shortened to Q8[2]	
	HDq12 (N=273)	HDq16 (N=139)	HDq12 (N=27)	HDq16 (N=6)
Age (years)				
n	273	139	27	6
Mean (SD)	62.2 (10.87)	62.0 (9.56)	59.1 (13.86)	55.2 (9.06)
Median	63.0	62.0	58.0	55.5
Min : Max	28 : 87	37 : 83	24 : 83	44 : 67
Race, n (%)				
American Indian or Alaska Native	2 (0.7%)	0	0	0
Asian	43 (15.8%)	20 (14.4%)	4 (14.8%)	0
Black or African American	28 (10.3%)	9 (6.5%)	4 (14.8%)	0
Native Hawaiian or Other Pacific Islander	1 (0.4%)	0	0	0
White	190 (69.6%)	107 (77.0%)	19 (70.4%)	6 (100%)
Multiple	1 (0.4%)	0	0	0
Other	4 (1.5%)	1 (0.7%)	0	0
Not Reported	4 (1.5%)	2 (1.4%)	0	0
Sex, n (%)				
Female	99 (36.3%)	57 (41.0%)	7 (25.9%)	3 (50.0%)
Male	174 (63.7%)	82 (59.0%)	20 (74.1%)	3 (50.0%)
BCVA (ETDRS letter score)				
n	273	139	27	6
Mean (SD)	63.9 (10.10)	62.7 (11.15)	59.4 (10.01)	53.3 (13.49)
Median	66.0	66.0	58.0	57.0
Min : Max	27 : 79	29 : 78	43 : 77	36 : 68
CRT (microns)				
n	272	139	27	6
Mean (SD)	444.9 (129.82)	447.1 (112.54)	511.4 (117.50)	530.2 (103.08)
Median	424.0	418.0	509.0	529.5
Min : Max	229 : 1309	255 : 768	333 : 835	347 : 650
Missing	1	0	0	0

BCVA=Best corrected visual acuity; CRT=Central retinal thickness; ETDRS=Early treatment diabetic retinopathy study; FAS=Full analysis set; Min=Minimum; Max=Maximum; n=Number of participants; N=Total number of participants; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks

[1] Maintained on Q12 or Q16 includes all participants randomized to HDq12 whose dosing interval was not shortened to Q8 through Week 48, and all participants randomized to HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48.

[2] Interval shortened to Q8 includes all participants randomized to HDq12 or HDq16 whose dosing interval was shortened from an assigned Q12 or Q16 regimen to Q8 (after 3 initial monthly doses) anytime through Week 48.

The percentage is based on the number of participants in each sub-population by treatment group as denominator.

See Definition of Terms for explanation of treatment groups.

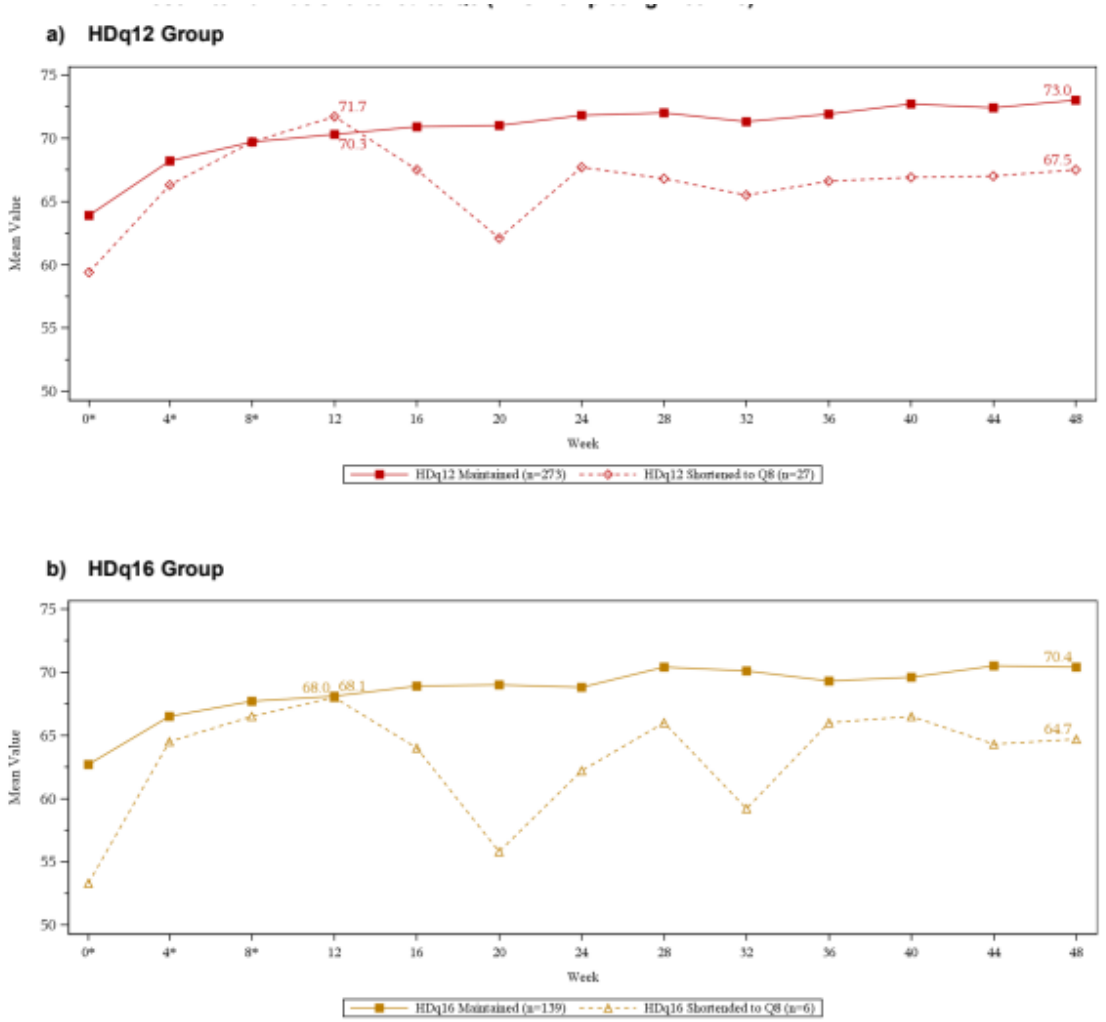
The proportion of participants in the PHOTON study appears to be similar across the different subgroups: those who maintained their randomized interval, those whose interval was shortened at any time, and those whose interval was shortened specifically to Q8 at any time. However, it is observed that the subgroup with intervals shortened to Q8 at any time is smaller in the HDq16 group (6 participants, 3.8%) compared to the HDq12 group (27 participants, 9.0%).

Concerning the demographics and baseline characteristics in participants in the PHOTON study, differences in demographic and baseline characteristics were noted between the subgroups of participants who had their dosing interval shortened from the originally assigned Q12 or Q16 regimen to Q8, and those who remained on their assigned Q12 or Q16 regimen. Baseline mean BCVA values ranged from 53.3 concerning the HDq16 with interval shortened to Q8 to 63.9 ETDRS letter for the HDq12 with maintained on Q12, while mean CRT values ranged from 444.9 µm concerning the HDq12 with maintained on Q12 to 530.2µm for HDq16 with interval shortened to Q8.

- ***Participants who maintained their randomized interval versus those whose dosing interval was shortened from an assigned Q12 or Q16 regimen to Q8***

    - **BCVA mean values and mean change from baseline**

Figure 24 displays the mean BCVA values, and Figure 25 presents the mean change from baseline in BCVA through Week 48 in the PHOTON study. These results are shown for the subgroups of participants randomized to the HDq12 and HDq16 groups who either maintained their assigned Q12 or Q16 dosing intervals or met the visual and anatomic DRM criteria for interval shortening, resulting in a dosing interval reduction from Q12 or Q16 to Q8.



* Initial monthly doses.

Note: In the HDq12 group, 27 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=3), Week 20 (n=12), or at subsequent dosing visits (n=12), and remained on Q8 through Week 48. In the HDq16 group, 6 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=1), Week 20 (n=3), or at subsequent dosing visits (n=2), and remained on Q8 through Week 48.

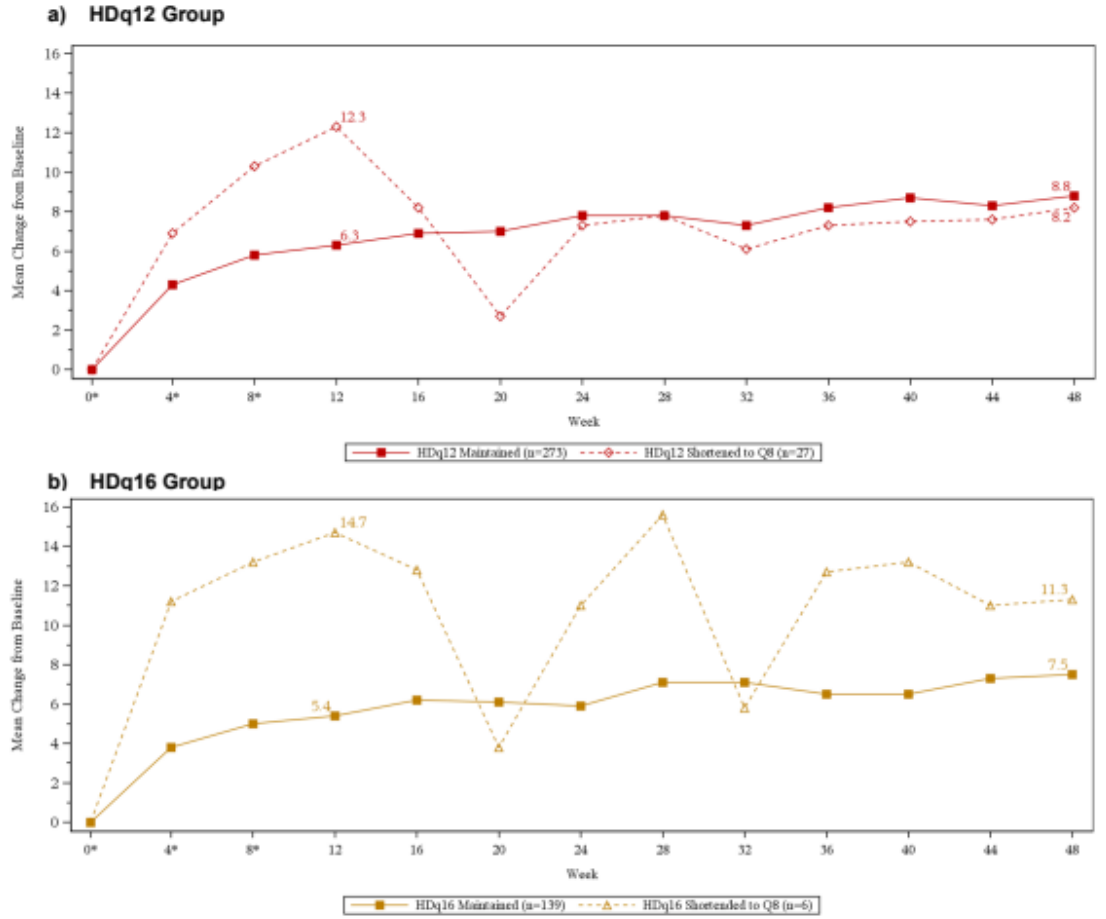
BCVA=Best corrected visual acuity; DRM=Dose regimen modification; FAS=Full analysis set; ICE=Intercurrent event; n=Number of participants; OC=Observed cases; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAP=Statistical analysis plan.

HDq12 maintained and HDq16 maintained includes all participants randomized to HDq12 or HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48. HDq12 shortened to Q8 and HDq16 shortened to Q8 includes all participants randomized to HDq12 or HDq16 who met visual and anatomic DRM criteria and whose dosing interval was shortened from an extended interval to Q8 (after 3 initial monthly doses) anytime through Week 48.

Observations after an ICE defined for the primary estimand were excluded as described in the SAP.

See Definition of Terms for explanation of treatment groups.

Figure 24: Mean BCVA (ETDRS Letters) by visit through week 48 in the HDq12 (a) and HDq16 (b) groups in participants in the PHOTON study who maintained a Q12 or Q16 dosing interval versus those whose interval was shortened to Q8 (FAS Completing week 48)



* Initial monthly doses.

Note: In the HDq12 group, 27 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=3), Week 20 (n=12), or at subsequent dosing visits (n=12), and remained on Q8 through Week 48. In the HDq16 group, 6 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=1), Week 20 (n=3), or at subsequent dosing visits (n=2), and remained on Q8 through week 48.

BCVA=Best corrected visual acuity; DRM=Dose regimen modification; FAS=Full analysis set; ICE=Intercurrent event; n=Number of participants; OC=Observed cases; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAP=Statistical analysis plan.

HDq12 maintained and HDq16 maintained includes all participants randomized to HDq12 or HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48. HDq12 shortened to Q8 and HDq16 shortened to Q8 includes all participants randomized to HDq12 or HDq16 who met visual and anatomic DRM criteria and whose dosing interval was shortened from an extended interval to Q8 (after 3 initial monthly doses) anytime through Week 48.

Observations after an ICE defined for the primary estimand were excluded as described in the SAP.

See Definition of Terms for explanation of treatment groups.

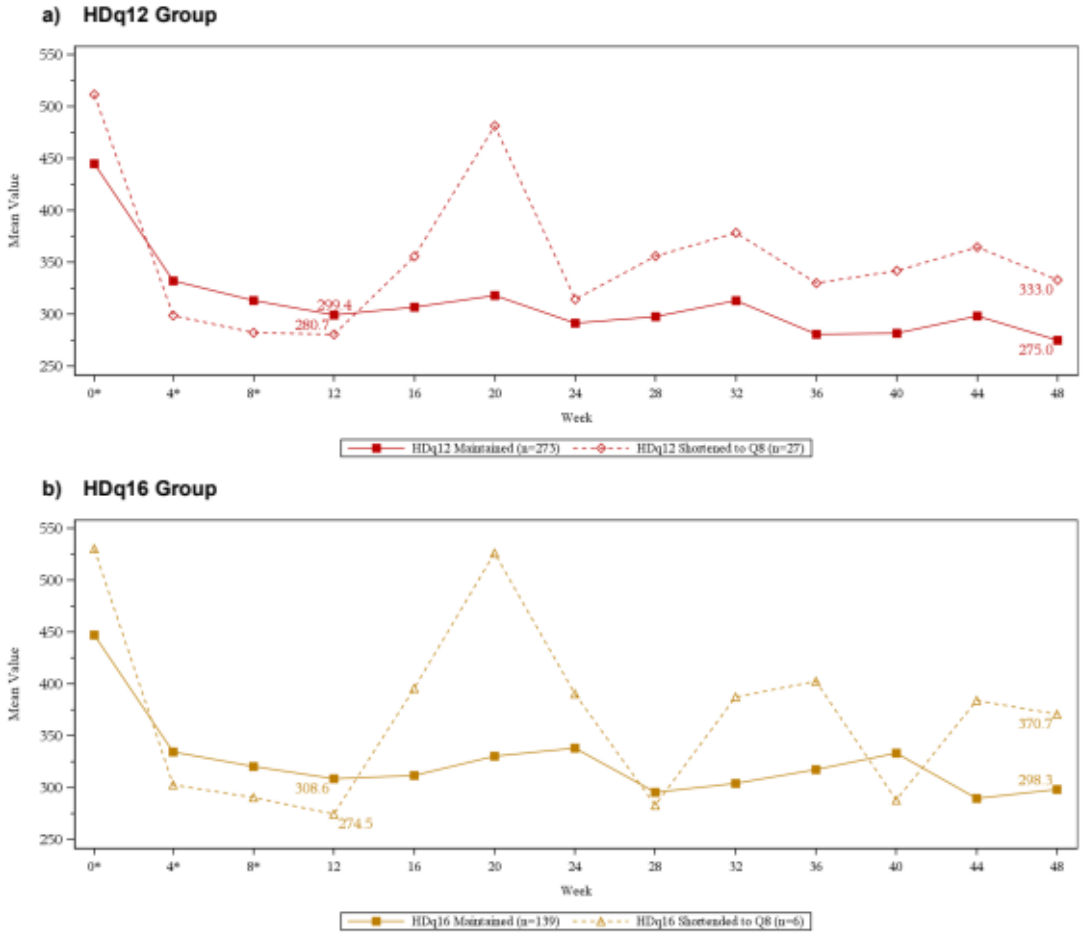
Figure 25: Mean change in BCVA (ETDRS Letters) by visit through week 48 in the HDq12 (a) and HDq16 (b) Groups in participants in the PHOTON study who maintained a Q12 or Q16 dosing interval versus those whose interval was shortened to Q8 (FAS Completing week 48)

From Week 16, in both the HDq12 and HDq16 groups, when the time between injections increased and 8 weeks had passed since the last HD aflibercept dose, participants in the HDq12 and HDq16 subgroups who met the criteria to switch to Q8 dosing experienced a decline in mean BCVA and also mean change from baseline. On average, they did not regain the vision improvements they had seen at Week 12.

Consequently, based on these data, the MAH concluded that more frequent dosing of aflibercept 8 mg may be necessary to preserve and/or improve vision in patients with treatment-resistant DME.

- **CRT: Mean values and mean changes from baseline**

Figure 26 shows the mean CRT values, and Figure 27 presents the mean change from baseline in CRT through Week 48 in the PHOTON study. These data are shown for subgroups of participants randomized to the HDq12 and HDq16 groups who either maintained their assigned Q12 or Q16 dosing intervals or met the visual and anatomic DRM criteria and had their dosing interval shortened from Q12 or Q16 to Q8.



* Initial monthly doses.

Note: In the HDq12 group, 27 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=3), Week 20 (n=12), or at subsequent dosing visits (n=12), and remained on Q8 through Week 48. In the HDq16 group, 6 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=1), Week 20 (n=3), or at subsequent dosing visits (n=2), and remained on Q8 through Week 48.

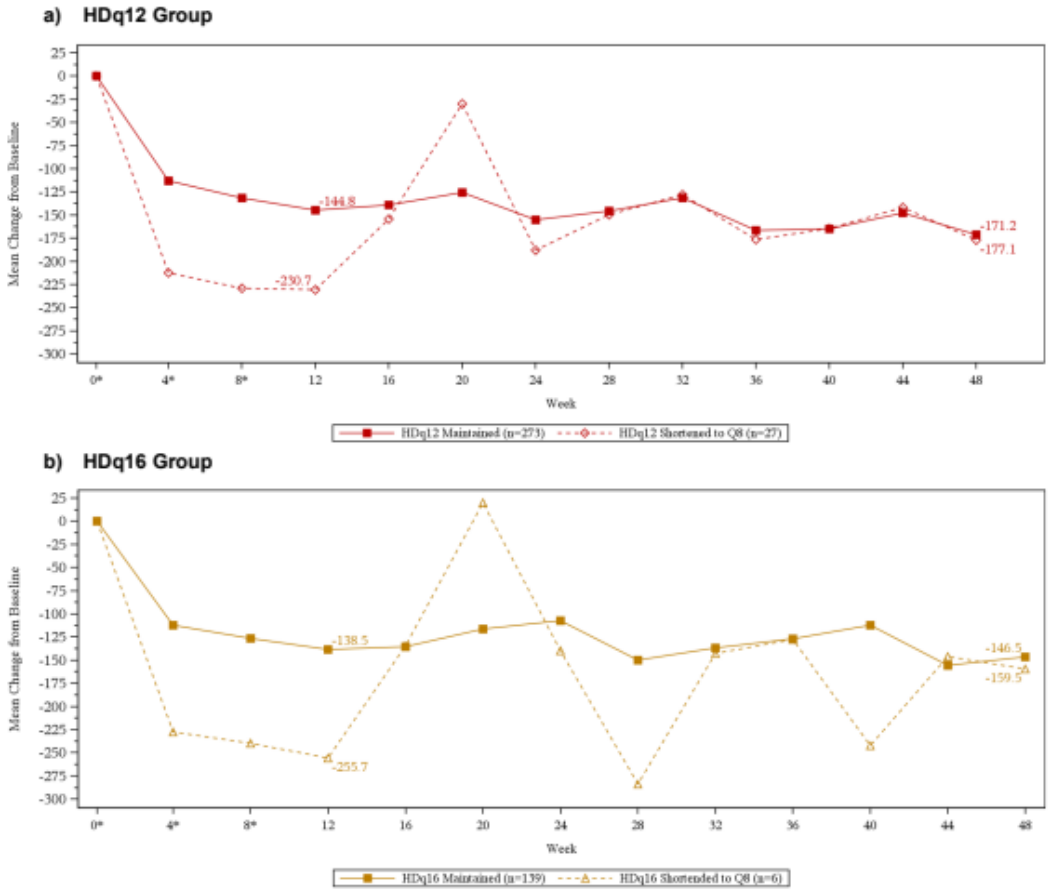
CRT=Central retinal thickness; DRM=Dose regimen modification; FAS=Full analysis set; ICE=Intercurrent event; n=Number of participants; OC=Observed cases; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAP=Statistical analysis plan.

HDq12 maintained and HDq16 maintained includes all participants randomized to HDq12 or HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48. HDq12 shortened to Q8 and HDq16 shortened to Q8 includes all participants randomized to HDq12 or HDq16 who met visual and anatomic DRM criteria and whose dosing interval was shortened from an extended interval to Q8 (after 3 initial monthly doses) anytime through Week 48.

Observations after an ICE defined for the primary estimand were excluded as described in the SAP.

See Definition of Terms for explanation of treatment groups.

Figure 26: Mean CRT (um) by visit through week 48 in the HDq12 (a) and HDq16 (b) groups in participants in the PHOTON Study who maintained a Q12 or Q16 dosing interval versus those whose interval was shortened to Q8 (FAS Completing week 48)



* Initial monthly doses.

Note: In the HDq12 group, 27 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=3), Week 20 (n=12), or at subsequent dosing visits (n=12), and remained on Q8 through Week 48. In the HDq16 group, 6 participants had their interval shortened to Q8; they received their first Q8 dose at Week 16 (n=1), Week 20 (n=3), or at subsequent dosing visits (n=2), and remained on Q8 through Week 48.

CRT=Central retinal thickness; DRM=Dose regimen modification; FAS=Full analysis set; ICE=Intercurrent event; n=Number of participants; OC=Observed cases; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAP=Statistical analysis plan.

HDq12 maintained and HDq16 maintained includes all participants randomized to HDq12 or HDq16 whose dosing interval was not shortened to Q8 or Q12 through Week 48. HDq12 shortened to Q8 and HDq16 shortened to Q8 includes all participants randomized to HDq12 or HDq16 who met visual and anatomic DRM criteria and whose dosing interval was shortened from an extended interval to Q8 (after 3 initial monthly doses) anytime through Week 48.

Observations after an ICE defined for the primary estimand were excluded as described in the SAP.

See Definition of Terms for explanation of treatment groups.

Figure 27: Mean change in CRT (um) by visit through week 48 in the HDq12 (a) and HDq16 (b) groups in participants in the PHOTON Study who maintained a Q12 or Q16 interval versus those whose interval was shortened to Q8 (FAS Completing week 48)

With regard to mean values and mean changes from baseline, a difference is observed between participants on Q8 dosing and those who maintained HDq12 or HDq16 regimens. The data show a non-linear trend in the group whose dosing interval was shortened from HDq12/HDq16 to Q8, compared to the group that maintained their original dosing schedule. Similar to findings in the PULSAR study, the group switched to Q8 dosing had a higher baseline CRT (approximately 520 µm) than the group that remained on HDq12 or HDq16, which had a baseline CRT of around 450 µm.

- ***Participants whose dosing interval was shortened to Q8 who continued to meet DRM criteria for interval shortening***

Table 83: Proportion of participants in the PHOTON Study whose dosing interval was shortened from Q12 or Q16 to Q8 and who continued to meet DRM criteria through Week 48 (SAF Completing Week 48)

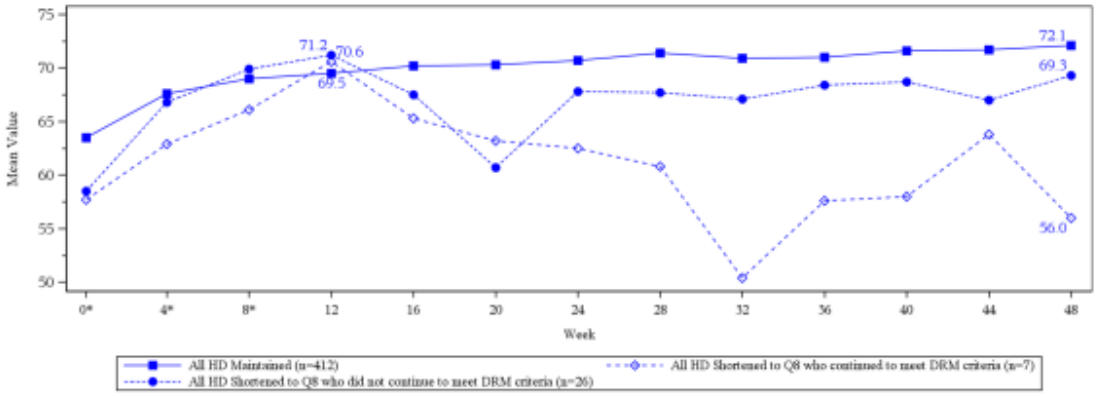
	2q8 (N=157)	HDq12 (N=300)	HDq16 (N=156)	All HD (N=456)
Participants who were shortened to Q8 and continued to meet DRM criteria, n (%)	7 (4.5%)	5 (1.7%)	2 (1.3%)	7 (1.5%)

DRM=Dose regimen modification; n=Number of participants; N=Total number of participants; Q4=Every 4 weeks; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks; SAF=Safety analysis set

Derived DRM used the same visual and anatomic criteria for shortening the dosing interval to Q8. Percentages of participants who completed Week 48 in the HDq12, HDq16, and 2q8 groups and continued to meet criteria (and would have had the dosing interval shortened to Q4) were based on participants whose dosing interval had already been shortened to Q8 at any time through Week 48 for the HD groups, and for all participants in the 2q8 group. The derived DRM criteria was met if there was a BCVA >10-letter loss from Week 12 AND CRT >50 µm increase from Week 12 at a scheduled dosing visit.

The percentage is based on the number of participants in each treatment group as denominator.

See Definition of Terms for explanation of treatment groups.



* Initial monthly doses.

DRM=Dose regimen modification; FAS=Full analysis set; n=Number of participants; N=Total number of participants; Q4=Every 4 weeks; Q8=Every 8 weeks; Q12=Every 12 weeks; Q16=Every 16 weeks

All HD maintained includes all participants in the HDq12 or HDq16 groups whose dosing interval was not shortened to Q8 or Q12 through Week 48. All HD to Q8 who did not continue to meet DRM criteria include all participants in the HDq12 or HD q16 groups who met DRM criteria and whose dosing interval was shortened to Q8 but did not continue to meet the derived DRM criteria through Week 48. All HD shortened to Q8 who continued to meet DRM criteria include all participants in the HDq12 or HD q16 groups who met DRM criteria and whose dosing interval was shortened to Q8 and continued to meet the derived DRM criteria through Week 48.

The derived DRM criteria was met if BCVA >10-letter loss from Week 12 AND CRT >50 µm increase from Week 12 at scheduled dosing visits.

Observations after an ICE defined for the primary estimand were excluded as described in the SAP.

See Definition of Terms for explanation of treatment groups.

Figure 28: Mean BCVA (ETDRS Letters) by visit through week 48 in the All HD group in the PHOTON Study in participants who maintained a Q12 or Q16 interval, those who met DRM criteria and whose dosing interval was shortened to Q8 but did not continue to meet DRM criteria, and those whose dosing interval was shortened to Q8 who continued to meet DRM criteria for further interval shortening (FAS Completing week 48)

When comparing Table 77 and Table 79, which show the proportion of participants in the PHOTON study treated with HD aflibercept who maintained their randomized interval through Week 48 versus those whose interval was shortened to Q8 after the initial monthly dosing phase (SAF Completing Week 48), it is observed that out of 34 participants (HDq12/HDq16 interval shortened to Q8 at any time), 7 (20.5%) continued to meet the DRM criteria, corresponding to 1.5% of all HD group. According to Figure 28, among the participants who met the DRM criteria for shortening to Q8, those who continued to meet these criteria had the lowest mean BCVA outcomes between Week 16 and Week 48.

Q4 dosing for patients with DME and nAMD:

To support a potential efficacy of shortening the treatment interval to 4 weeks, the Applicant relies on three studies: one based on modelling and simulations, and two based on real-world data.

Modelling and simulation:

The conclusions drawn from these simulated trials are that the subset of participants with nAMD or DME who continued to meet DRM criteria after their dosing interval was shortened to Q8 showed further improvements in CST and BCVA when their dosing interval was subsequently reduced to Q4, compared with participants who remained on a Q8 interval.

SPECTRUM

SPECTRUM is a global, prospective, observational study aimed at assessing the real-world effectiveness of intravitreal aflibercept 8 mg in patients with nAMD or DME, either treatment-naïve or previously treated, in routine clinical practice.

Enrolment started on 15 February 2024 and was completed by 30 September 2025. Overall, 3739 patients with naïve or previously treated neovascular nAMD or DME were enrolled and are planned to be observed for 24 months.

The focus was on the results corresponding to the Applicant's variation request, namely a reduction of the injection interval to 4 weeks. Furthermore, in order to align as closely as possible with the studies previously submitted by the Applicant (PHOTON and PULSAR), only treatment-naïve patients were considered.

Naive nAMD and Naïve DME:

The results provided by the Applicant suggest a stabilization of visual acuity as well as of CRT over time in treatment-naïve patients who required intervals shorter than Q8. Equivalent results were observed in patients with DME.

However, it should be noted that these evaluations included patients whose dosing interval was reduced to Q4 as well as to Q6.

To conclude, the latest data provided by the Applicant have proven to be convincing:

Further details were requested concerning the data from the SPECTRUM and FRB! studies.

For the SPECTRUM study, the Applicant was asked to provide data highlighting the efficacy of the treatment in treatment-naïve patients who, after the initiation phase, received one or more doses of aflibercept 8 mg at 4-week intervals. Additionally, the results were to be compared with those obtained in the treatment-naïve population who did not require a reduction of the treatment interval to 4 weeks.

Concerning the FRB! Study, the Applicant was requested to provide complementary information, particularly on the reduction of aflibercept 8 mg injection intervals to 4 weeks for patients requiring a dose adjustment, and to compare the efficacy of these patients with those not requiring a dose adjustment.

To support its argument, the Applicant emphasized that it is more appropriate to compare patients treated with frequent injections and intensive therapy to untreated patients, rather than directly comparing outcomes between patients receiving intensive versus less intensive treatment. Such a direct comparison can be biased, as these are self-selected groups based on their response to treatment. Patients treated more frequently may have more severe disease and/or may be more difficult to treat, while those treated at longer intervals may have a more pronounced response to treatment and therefore achieve a benefit with longer intervals.

SPECTRUM:

SPECTRUM is an ongoing, global, prospective, observational study designed to evaluate the real-world effectiveness of intravitreal aflibercept 8 mg in patients with neovascular age-related macular degeneration (nAMD) or diabetic macular edema (DME). The study includes both treatment-naïve patients and those previously treated, reflecting routine clinical practice.

The study evaluated different dosing interval groups (<8 weeks, 4 weeks, 6 weeks, and ≥8 weeks) and the data reported for these respective groups include:

- Change in visual acuity letters score from baseline to Month 12
- Visual acuity letters score at Month 12
- Change in central retinal thickness (CRT; µm) from baseline to Month 12
- CRT (µm) at Month 12

The data provided by the Applicant support the efficacy of the treatment when the dosing interval is reduced to less than 8 weeks. Indeed, the observed outcomes are equivalent to those seen in patients who did not require a dosing interval of less than 8 weeks, for both patients previously treated or naive with neovascular age-related macular degeneration (nAMD) and those with diabetic macular edema (DME).

It is also agreed that the option to reduce the dosing interval to less than 8 weeks provides an additional treatment choice for patients refractory to Q8 dosing. This flexibility is valuable, and if the shorter interval does not prove effective, patients can then switch to other therapies.

FRB!

This is an advanced, web-based ophthalmic registry designed to collect and track clinical practice data and outcomes for retinal diseases—including neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME)—across multiple countries. However, The Applicant has submitted results for neovascular age-related macular degeneration (nAMD) only, as the data for diabetic macular edema (DME) are insufficient. Overall, the data provided by the Applicant for this study are limited. The data from this study are not necessarily interpretable due to their limited scope and the fact that they focus solely on one condition (nAMD). However, this study primarily supports the observation that, in routine clinical practice, dose interval shortening is commonly implemented.

In conclusion, regarding the data provided by the Applicant, the results are conclusive in demonstrating a therapeutic benefit for patients who are refractory to longer dosing intervals for patient suffering from nAMD and DME.

Summary of main study(ies)

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 84: Summary of Efficacy for trial QUASAR Study – 22153

Title: QUASAR			
Study identifier	**QUASAR Study - 22153**		
Design	is an ongoing[#], multi-center, randomized, double-masked, three-arm, active-controlled clinical trial designed to evaluate the efficacy and safety of high-dose (8 mg) intravitreal aflibercept compared to the approved 2 mg dose in patients with treatment-naïve macular edema resulting from retinal vein occlusion (RVO).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		64 Weeks not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	2q4		aflibercept 2 mg administered every 4 weeks until Week 32, followed by adjustment of treatment intervals according to treatment response.
	8q8/3		aflibercept 8 mg administered every 8 weeks, with possible interval adjustments based on Dose Regimen Modifications criteria, following an initial loading phase of 3 injections given at 4-week intervals.
	8q8/5		aflibercept 8 mg administered every 8 weeks, with possible interval adjustments based on Dose Regimen Modifications criteria, following an initial loading phase of 5 injections given at 4-week intervals.
Endpoints and definitions	Primary endpoint		Change from baseline in BCVA measured by the ETDRS letter score at Week 36
	Key secondary efficacy endpoints		Number of active injections from baseline to Week 64

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

[#]At the time of the variation submission, the study was still ongoing and was completed before the end of this procedure.

2.4.2. Discussion on clinical efficacy

The MAH submitted a grouped type II variation for Eylea 114.3 mg/ml to update the product information:

- A type II variation under category C.I.6.a has been submitted to extend the therapeutic indication to include the treatment of macular edema secondary to retinal vein occlusion (RVO), supported on the results of the pivotal Phase III study 22153 (QUASAR). Accordingly, updates have been made to sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC, and the package leaflet has been revised to reflect these changes.
- A type II variation (C.I.4) has been submitted to revise the minimum treatment interval in SmPC section 4.2 for nAMD and DME, based on data from study 22153 (QUASAR) and post-hoc analyses of studies 20968 (PULSAR), 21091 (PHOTON), and 21086 (CANDELA).

Eylea 114.3 mg/ml: Treatment of macular oedema secondary to retinal vein occlusion (QUASAR)

This submission proposes a new indication, RVO, and an update to the approved dosing regimen for nAMD and DME in the maintenance phase to provide the option for monthly dosing (Q4).

The new indication, RVO, as proposed by the MAH, is intended to lessen the treatment burden for both patients and healthcare professionals by reducing the number of injections and clinic visits.

QUASAR was a multicenter, randomized, double-masked, three-arm, active-controlled clinical trial designed to assess the efficacy and safety of high-dose intravitreal aflibercept (8 mg) compared to the approved 2 mg dose in patients with treatment-naïve macular edema secondary to retinal vein occlusion (RVO). In QUASAR study, patients were randomized in a 1:1:1 ratio to receive monotherapy in the treated eye with either 2 mg aflibercept (administered every 4 weeks until week 32, followed by adjustment of treatment intervals according to treatment response) or aflibercept 8 mg 8q8/3 or 8q8/5

(administered every 8 weeks after 3 initial Q4W or administered every 8 weeks after 5 initial Q4W).The participants could benefit from a dose regimen modification

Inclusion and exclusion criteria appear relevant to select appropriately patients with CRVO, BRVO or HRVO, in accordance with previous clinical studies like COPERNICUS, GALILEO concerning CRVO and VIBRANT concerning BRVO. It is fully supported that the selection criteria should not exclude patients with ischemic RVO.

Concerning, the participants flow chart, the number of patients randomized appears well-balanced across treatment groups. However, a higher number of patients who did not complete the study until Week 36 in the 8q8/5 group (23, 7.7%) compared to the 8q8/3 group (13, 4.4%) and the 2q4 group (14, 4.6%). This elevated non-completion rate in the 8q8/5 group is primarily due to a higher number of subject withdrawals (16, 5.4%) compared to the 8q8/3 group (8, 2.7%) and the 2q4 group (8, 2.6%). Given these observations, especially the twofold higher subject withdrawal rate in the 8q8/5 group, the Applicant was requested to justify these differences. Clarification was sought regarding the discrepancy between Tables concerning the primary reason and total number of subjects who did not complete the study until Week 36. The Applicant argued that as specified in the Clinical Study Protocol, participants who discontinued treatment were permitted to remain in the study. Consequently, the number of participants who discontinued from the study is lower than the number who discontinued from treatment which correspond to the difference observed.

A total of 168 participants (18.8%) experienced major protocol deviations. The most common deviations (≥5%) were related to treatment. Based on the data provided by the Applicant, a higher number of important protocol deviations was observed in the 8q8/3 group (63 patients, 21.4%) and the 8q8/5 group (60 patients, 20.1%) compared to the 2q4 group (45 patients, 14.9%).

When analyzing the different categories of major deviations, most appear to be relatively balanced across the treatment groups — except for treatment-related deviations. Notably, treatment deviations occurred more frequently in the 8q8/3 group (43 patients, 14.6%) compared to the 2q4 and 8q8/5 groups (30 patients [9.9%] and 25 patients [8.4%], respectively).

According to table 9, the most common reported treatment deviation was related to participants not being extended despite meeting the extension criteria.

Given this discrepancy, the Applicant was requested to clarify why the most frequently reported treatment deviation involved participants not being extended despite fulfilling the extension criteria, and in particular, to explain why such deviations were more frequent in the 8q8/3 group (e.g., due to staff oversight, insufficient training, etc.). The Applicant emphasized that, according to the dosing schedule outlined in the Clinical Study Protocol, participants in the 8q8/3 and 2q4 groups were allowed to extend their dosing intervals starting at Week 32, whereas participants in the 8q8/5 group were not permitted to do so until Week 40. Consequently, a protocol deviation involving interval extensions through Week 36 could only occur in the 8q8/3 and 2q4 groups, and not in the 8q8/5 group.

Moreover, according to the data provided by the Applicant, participants in the 8q8/3 and 2q4 groups who met the criteria but were not extended showed a balanced distribution between the two groups (19 vs. 16 participants).

Also, according to the data provided by the Applicant at week 64, the treatment deviations are well balanced between each group of treatment (2q4, 8q8/3, 8q8/5) with a slight higher frequency concerning the 2q4 group (62 patients, 20.5%) and the group 8q8/3 (62 patients, 21.1%) compared to the 8q8/5 group (52 patients, 17.4%).

Given the relatively high rate of patients presenting with important protocol deviation (19%) and the context of a non-inferiority trial, an analysis of the primary endpoint in the per-protocol population

(excluding these above patients) was asked to be carried out as sensitivity analysis. The sponsor provided the requested analysis on the population that adhered most closely to the protocol. It showed a very limited impact on the initial results, with a loss of one letter in terms of point estimates and precision (lower limit of the 95% CI) which does not jeopardize the non-inferiority of the new treatment modalities (8q8/3 and 8q8/5) compared to the control modality (2q4) and fully supports the robustness of the primary analysis conclusion.

Moreover, the primary objective of the study, which was to determine if treatment with aflibercept 8mg Q8 provides non-inferior BCVA change compared to aflibercept 2mg Q4, is supported for the assessment of non-inferiority and is in line with the initial Scientific Advice EMA/SA/0000086937. Furthermore, Subgroup analyses show results consistent with the overall result. Of note the better homogeneity of subgroups for the 8 mg/5 for which almost all subgroups (88%=21/24) achieve the non-inferiority despite their smaller size.

Secondary efficacy endpoints evaluate the number of active injections, change in BCVA, CST, presence/absence of intra/sub-retinal fluid from baseline at different time points over the study course. The secondary efficacy endpoints are therefore deemed acceptable.

Concerning the result, the primary efficacy endpoint was the change from baseline in best-corrected visual acuity (BCVA), measured by the ETDRS letter score at Week 36, which correspond to determine if treatment with aflibercept 8 mg Q8 provides non-inferior BCVA change compared to aflibercept 2 mg Q4. According to the data provided by the Applicant, the primary objective is met at week 36 for QUASAR study, concerning 8q8/3 and 8q8/5 treatment. In fact, for the 8q8/3, the non-inferiority of Eylea 8q8/3 to Eylea 2q4 for the primary endpoint, BCVA change from baseline at week 36 in the study eye, is confirmed with a non-inferiority margin letters ($p<0.001$, assessed at a one-sided significance level of 0.025). Moreover, concerning the 8q8/5 group, the non-inferiority of Eylea 8q8/5 to Eylea 2q4 for the primary endpoint, BCVA change from baseline at week 36 in the study eye, is confirmed with a non-inferiority margin letters ($p<0.001$, assessed at a one-sided significance level of 0.025).

The Applicant has provided the requested information up to week 64, and it is therefore concluded that the 8q8/3 treatment regimen demonstrates non-inferiority compared to the 2q4 regimen. From this perspective, the primary endpoint is therefore met. Furthermore, it is also agreed that the key secondary endpoint is achieved, highlighting the superiority of the 8q8/3 regimen over 2q4.

In conclusion, non-inferiority has been observed between the 2q4 and 8q8/3 regimens.

Concerning the secondary efficacy endpoint at Week 36: Number of active injections from baseline to week 36, Gain of ≥15 letters from baseline at week 36, EDTRS letter score of ≥69 at week 36, No IRF and no SRF in central subfield at week 36, CST change from baseline at week 36, CST change from baseline at week 36, Change from baseline in NEI-VFQ-25 total score at week 36. The secondary endpoints are presented in the Table 80. All of these elements are consistent in demonstrating that there is no clinically meaningful difference and thus support the non-inferiority of aflibercept 8 mg Q8 compared to aflibercept 2 mg Q4 at week 36 and week 64.

The Applicant provided efficacy and safety data up to 64 weeks which also correspond to several secondary endpoint including the key secondary efficacy endpoint corresponding to the number of active injections from baseline to Week 64. A justification concerning the decrease in efficacy, notably for the measurement of BCVA in the 8q8/3 and 8q8/5 treatment groups, and also a decline in efficacy observed across the different RVO subgroups at various time points was provided. In this way, the Applicant highlighted that, in the 8q8/3 arm, patients had the opportunity at Weeks 16, 24, and 32 to increase the frequency of injections from Q8 to Q4 if they met protocol-specified criteria for shortening the interval, based on loss of initial visual and anatomical improvements. In the 8q8/5 arm, patients had the same opportunity at Weeks 24 and 32. This argument is fully supported and corresponds to

the various observed time points, confirming the possibility of reducing the treatment interval. It was also noted and accepted that, as shown in Figures 10A and 10B, shortening the treatment interval in the QUASAR study allowed recovery of visual gain.

Similarly, regarding the observed variations and the decrease in efficacy for CST at Weeks 16, 24, and 32, it is fully acknowledged that these correspond to fluctuations due to the need to increase the treatment frequency in certain patients.

Eylea 8mg Q4 dosing

This submission proposes an update to the approved dosing regimen for nAMD and DME in the maintenance phase to provide the option for monthly dosing (Q4).

Shortening term dosing recommendations in the pivotal study QUASAR

Participants in the 8 mg groups started with monthly dosing regimens, receiving 3 or 5 initial monthly injections. Following this initial phase, participants in the high-dose (HD) group had their dosing interval extended to every 8 weeks. However, to account for potential variability in treatment response, the study permitted shortening of the dosing interval to Q4 starting at Week 16 for the 8q8/3 group and at Week 24 for the 8q8/5 group, in participants who met protocol-defined DRM criteria based on a loss of the visual and anatomic improvements achieved during the initial monthly dosing phase.

Analysis of clinical information relevant to dosing recommendations

According to the data provided by the Applicant, shortening the dosing interval for participants who met the protocol-defined DRM criteria may suggest a potential visual benefit. Indeed, the data indicate that from Week 16 for the 8q8/3 group and from Week 24 for the 8q8/5 group, improvements in BCVA and CST were observed, resulting in values returning to levels comparable to those of participants who did not require a dosing interval shortening (8q8/3 and 8q8/5 maintained).

Shortening term dosing recommendations in the pivotal studies PULSAR and PHOTON

Both pivotal studies, PULSAR and PHOTON, were multicenter, randomized, double-masked, parallel-group, active-controlled trials conducted from baseline through Week 96. They evaluated the efficacy and safety of high dose (HD) aflibercept administered at extended dosing intervals (every 12 weeks [HDq12] or every 16 weeks [HDq16]) compared to the approved 2 mg aflibercept dose administered every 8 weeks (2q8) (Table 81).

Table 85: Dosing schedules in the PULSAR and PHOTON studies

Year 1 (main study)

		D1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
PULSAR	2q8	x	x	x	---	x	o	x	o	x	o	x	o	x
	HDq12	x	x	x	---	o	x	o	o	x	o	o	x	o
	HDq16	x	x	x	---	o	o	x	o	o	o	x	o	o
PHOTON	2q8	x	x	x	x	x	o	x	o	x	o	x	o	x
	HDq12	x	x	x	o	o	x	o	o	x	o	o	x	o
	HDq16	x	x	x	o	o	o	x	o	o	o	x	o	o

In both studies, dosing intervals were modified according to protocol-defined criteria of disease progression.

During the first year of treatment, starting at Week 16, injection intervals for participants assigned to HDq12 or HDq16 could be shortened based on DRM criteria (Table 82):

- If a participant in the HDq12 group or the HDq16 group met DRM criteria at Week 16 or Week 20, the participant was dosed with HD aflibercept at that visit and subsequently continued receiving HD aflibercept every 8 weeks.
- A participant in the HDq16 group who had not met DRM criteria at Week 16 or Week 20 and met DRM criteria at Week 24 was dosed with HD aflibercept at that visit and subsequently continued receiving HD aflibercept every 12 weeks.
- Subsequently, participants who met DRM criteria at any active treatment visit had their intervals shortened by 4 weeks, to a minimum interval of 8 weeks.

Table 86: Criteria for dose regimen modifications (DRMs)

		PULSAR	PHOTON
Year 1	**Shortening** Beginning at Week 16	• BCVA loss >5 letters from Week 12 **and** • Any of the following – CRT increase >25 µm from Week 12 – New foveal hemorrhage – New foveal neovascularization	• BCVA loss >10 letters from Week 12 in association with persistent or worsening DME **and** • CRT increase >50 µm from Week 12
	Extending	*No extension during Year 1*	*No extension during Year 1*

All participants were examined every 4 weeks through Week 96.

Analysis of clinical information relevant to dosing recommendations

Data from the pivotal PULSAR and PHOTON studies highlight that, starting at Week 16, in both the HDq12 and HDq16 groups, when the interval between injections was extended and 8 weeks had passed since the last HD aflibercept dose, participants in the HDq12 and HDq16 subgroups who had met the criteria to switch to Q8 dosing experienced a decline in both mean BCVA and mean change from baseline. On average, these participants did not recover the visual gains achieved at Week 12.

In both the PHOTON and PULSAR studies, differences in mean CRT values and changes from baseline were observed between participants on Q8 dosing and those who maintained HDq12 or HDq16 regimens. In PHOTON, a non-linear trend was noted in the group switched to Q8, which also had a higher baseline CRT (~520 µm) compared to those who remained on HDq12/HDq16 (~450 µm). In PULSAR, CRT outcomes were generally similar across groups, although a greater mean change from baseline was observed in the HDq16 group shortened to Q8. However, this finding must be interpreted with caution, as the Q8 group had a higher baseline CRT (~450 µm) than the HDq16 maintained group (~350 µm).

Consequently, based on these data, the Applicant concluded that more frequent dosing of aflibercept 8 mg may be necessary to preserve and/or improve vision in patients with treatment-resistant nAMD and DME. In the QUASAR, PULSAR, and PHOTON studies, the results indicate a possible need to shorten the dosing interval.

The submitted studies indicate that only a small subgroup requires a 4-week treatment interval; however, QUASAR results suggest that these patients may benefit clinically from such an adjustment.

The real-world data provided by the Applicant have proven to be convincing, particularly the SPECTRUM study. SPECTRUM is an ongoing, global, prospective, observational study designed to evaluate the real-world effectiveness of intravitreal aflibercept 8 mg in patients with neovascular age-

related macular degeneration (nAMD) or diabetic macular edema (DME). The study includes both treatment-naïve patients and those previously treated, reflecting routine clinical practice.

In view of these data, the results are conclusive in demonstrating a therapeutic benefit for patients who are refractory to longer dosing intervals for patient suffering from nAMD and DME.

In this sense, there remained only one request that impacted the product's SmPC in section 4.2:

it was requested to include an addition in section 4.2 of the SmPC, under the 'Posology' subsection for 'nAMD and DME', as follows:

"The interval between 2 injections should not be shorter than 1 month. If visual and/or anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea 114.3 mg/ml should be discontinued.".

This request for an addition in section 4.2 of the SmPC was taken into account by the applicant and accepted.

2.4.3. Conclusions on the clinical efficacy

In summary, the QUASAR study was successful in terms of its stated aims and the clinical efficacy of Eylea 8mg in RVO has been demonstrated.

Concerning the q4 dosing, clarifications were provided by the Applicant, and they were convincing.

To conclude, all requests have been resolved.

2.5. Clinical safety

Introduction

In the current submission, the MAH provided the Week 36 and Week 64 (end of study) safety data of the Study 22153 a randomized, double-masked, active-controlled Phase 3 study of the efficacy and safety of aflibercept 8 mg in macular edema secondary to retinal vein occlusion (QUASAR) to support the inclusion of the new indication (RVO) for Eylea 8 mg (114.3 mg/mL). The MAH also provided a rational in order to change posology recommendations of the approved indications nAMD and DME based on the results from study 22153 (QUASAR) and post-hoc analysis of the pivotal studies 20968 (PULSAR), 21091 (PHOTON) and Phase II study 21086 (CANDELA).

Table 87: Study supporting the safety of HD RVO

Study identifier (Study no.)/Status	Study design	Study objectives	Number of participants in the SAF per treatment arm and total
QUASAR (Study 22153) / Ongoing (Last Participant Last Week 36 Visit: 07 NOV 2024)	Phase-3, multi-center, randomized, double-masked, active-controlled Treatment duration: 60 weeks Study duration: up to 67 weeks including screening phase (3 weeks) and EoS (Week 64)	Primary: To determine if treatment with aflibercept 8 mg Q8 provides non-inferior BCVA change compared to aflibercept 2 mg Q4 Secondary: • To determine if treatment with aflibercept 8 mg Q8 requires less injections compared to aflibercept 2 mg Q4 • To determine the effect of aflibercept 8 mg Q8 compared to aflibercept 2 mg Q4 on other visual and anatomic measures of response • To assess the efficacy of aflibercept 8 mg Q8 compared to aflibercept 2 mg aflibercept Q4 on vision-related QoL • To evaluate the safety of aflibercept 8 mg Q8 compared to aflibercept 2 mg aflibercept Q4 • To evaluate duration of effect of aflibercept 8 mg Q8 compared to aflibercept 2 mg aflibercept Q4 • To evaluate the PK of aflibercept 8 mg Q8 compared to aflibercept 2 mg aflibercept Q4	2q4: N=301 8q8/3: N=293 8q8/5: N=298 Total: N=892

For QUASAR, safety was analyzed using the safety analysis set (SAF), which included all participants randomly assigned to study intervention who were exposed to study intervention (active or sham injection) at least once. Analysis of the SAF was performed according to the treatment the participant received (as treated). Safety variables assessed were TEAEs (ocular and non-ocular), ocular examinations (e.g., intraocular pressure [IOP] measurement), physical examinations, vital signs, clinical laboratory tests, electrocardiograms (ECGs), and pregnancy testing.

The high dose of aflibercept (HD, 8 mg or 114,3 mg/mL) has been approved in EU in 2024 (EMEA/H/C/002392/X/0084/G) for the indications nAMD and DME. In this submission, the request for approval of the indication macular oedema secondary to retinal vein occlusion (RVO), which is already present for Eylea 2 mg, is based on the safety data up to 36 weeks of QUASAR, a randomized, double-masked, active-controlled Phase 3 study comparing 2q4 (Aflibercept 2 mg every 4 weeks until Q32) with 8q8/3 (Aflibercept 8 mg with 3 initial every 4 weeks followed by every 8 weeks) and 8q8/5 (Aflibercept 8 mg with 5 initial every 4 weeks followed by every 8 weeks) in participants with treatment-naïve macular oedema secondary to RVO. The applicant also provided the safety data up to 64 weeks.

The safety analysis set included all participants who had received at least one dose of study intervention (n = 892). The HD groups (i.e. 8q8/3 and 8q8/5) were pooled into the All 8 mg group. The SAF was identical to the FAS. The proposed safety plan is adequate.

Patient exposure

Overall extent of exposure and disposition

Of the 894 randomized participants, 892 (99.8%) participants were treated and included in the SAF, and 838 (93.7%) participants completed the study through Week 36. There were no notable differences between the treatment groups with regards to the reasons for premature discontinuation (Table 84).

Table 88: Completion of overall study: week 36 (all randomized participants)

Number of Participants	2q4 N=302 (100%)	8q8/3 N=294 (100%)	8q8/5 N=298 (100%)	All 8mg N=592 (100%)	Total N=894 (100%)
Randomized	302 (100.0%)	294 (100.0%)	298 (100.0%)	592 (100.0%)	894 (100.0%)
Treated	301 (99.7%)	293 (99.7%)	298 (100.0%)	591 (99.8%)	892 (99.8%)
Completed study through Week 36	287 (95.0%)	278 (94.6%)	273 (91.6%)	551 (93.1%)	838 (93.7%)
Did not complete study through Week 36	14 (4.6%)	13 (4.4%)	23 (7.7%)	36 (6.1%)	50 (5.6%) [a]
Primary reason					
Adverse event	2 (0.7%)	0	1 (0.3%)	1 (0.2%)	3 (0.3%)
Death	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)	7 (0.8%)
Lost to follow-up	2 (0.7%)	2 (0.7%)	2 (0.7%)	4 (0.7%)	6 (0.7%)
Physician decision	0	1 (0.3%)	0	1 (0.2%)	1 (0.1%)
Protocol deviation	0	0	1 (0.3%)	1 (0.2%)	1 (0.1%)
Withdrawal by subject	8 (2.6%)	8 (2.7%)	16 (5.4%)	24 (4.1%)	32 (3.6%)

Participants who completed the study are those who were followed for the duration of the study, irrespective of permanent discontinuation of study intervention.
a: No information was available on whether follow-up was completed or not for 4 participants (2 each in 8q8/3 and 8q8/5

Overall, 894 participants at 237 sites were randomized and 892 participants were treated. Of these, 795 participants completed the treatment phase through Week 64. 98 participants did not complete the study through Week 64, with no notable differences across the treatment groups with regards to the reasons for premature discontinuation. The most common reason for discontinuation was withdrawal by subject (Table 85).

Table 89: Disposition: Study participation through week 64 (all randomized participants)

Number (%) of subjects	2q4 N = 302 (100%)	8q8/3 N = 294 (100%)	8q8/5 N = 298 (100%)	All 8 mg N = 592 (100%)	Total N = 894 (100%)
Randomized	302 (100.0%)	294 (100.0%)	298 (100.0%)	592 (100.0%)	894 (100.0%)
Treated	301 (99.7%)	293 (99.7%)	298 (100.0%)	591 (99.8%)	892 (99.8%)
Completed study through Week 64	270 (89.4%)	268 (91.2%)	256 (85.9%)	524 (88.5%)	794 (88.8%)
Did not complete study through Week 64	31 (10.3%)	25 (8.5%)	42 (14.1%)	67 (11.3%)	98 (11.0%)
Primary reason					
Withdrawal by subject	18 (6.0%)	13 (4.4%)	28 (9.4%)	41 (6.9%)	59 (6.6%)
Lost to follow-up	5 (1.7%)	4 (1.4%)	5 (1.7%)	9 (1.5%)	14 (1.6%)
Death	3 (1.0%)	2 (0.7%)	5 (1.7%)	7 (1.2%)	10 (1.1%)
Adverse event	3 (1.0%)	2 (0.7%)	3 (1.0%)	5 (0.8%)	8 (0.9%)
Protocol deviation	0	0	1 (0.3%)	1 (0.2%)	1 (0.1%)
Physician decision	0	2 (0.7%)	0	2 (0.3%)	2 (0.2%)
Logistical problem	2 (0.7%)	2 (0.7%)	0	2 (0.3%)	4 (0.4%)

Participants who completed the study are those who were followed for the duration of the study, irrespective of permanent discontinuation of study intervention.
See Definition of terms for treatment group description

Exposure in the study eye

The mean number of active injections through Week 36 in the SAF population was 8.5, 6.0 and 6.7 in the 2q4, 8q8/3 and 8q8/5 treatment groups, respectively (Table 86). For those 838 participants completing Week 36 (Week 36 completers), the mean number of active injections was 8.8, 6.1 and 6.9 in the 2q4, 8q8/3 and 8q8/5 treatment groups, respective. Among the Week 36 completers, the target dosing interval of Q8 was maintained through Week 36 in 90.9% of participants in the All 8mg group. Through Week 36, a small portion of participants required more frequent treatment with treatment

intervals being shortened to Q4 (6.1% [for 8q8/3 group only] at Week 16, 4.2% at Week 24 and 1.8% at Week 32 [both for the All 8mg group]) (Table 87).

No substantial differences in the exposure to study intervention were observed across the different RVO types (CRVO/HRVO vs. BRVO).

Table 90: Exposure to study intervention in the study eye through week 36 (safety analysis set)

	2q4 N = 301 (100%)	8q8/3 N = 293 (100%)	8q8/5 N = 298 (100%)	All 8 mg N = 591 (100%)
Total number of active injections	2564	1746	1991	3737
Total number of sham injections	0	789	524	1313
Number of active injections				
1	2 (0.7%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
2	2 (0.7%)	1 (0.3%)	5 (1.7%)	6 (1.0%)
3	6 (2.0%)	3 (1.0%)	4 (1.3%)	7 (1.2%)
4	2 (0.7%)	5 (1.7%)	3 (1.0%)	8 (1.4%)
5	4 (1.3%)	17 (5.8%)	12 (4.0%)	29 (4.9%)
6	4 (1.3%)	241 (82.3%)	19 (6.4%)	260 (44.0%)
7	7 (2.3%)	10 (3.4%)	243 (81.5%)	253 (42.8%)
8	27 (9.0%)	14 (4.8%)	10 (3.4%)	24 (4.1%)
9	247 (82.1%)	0	0	0
Number of active injections				
N	301	293	298	591
Mean (SD)	8.5 (1.4)	6.0 (0.8)	6.7 (1.1)	6.3 (1.0)
Median (min, max)	9.0 (1, 9)	6.0 (1, 8)	7.0 (1, 8)	6.0 (1, 8)
Number of sham injections				
0	301 (100.0%)	5 (1.7%)	21 (7.0%)	26 (4.4%)
1	0	23 (7.8%)	30 (10.1%)	53 (9.0%)
2	0	29 (9.9%)	247 (82.9%)	276 (46.7%)
3	0	236 (80.5%)	0	236 (39.9%)
Number of sham injections				
N	301	293	298	591
Mean (SD)	0.0 (0.0)	2.7 (0.7)	1.8 (0.6)	2.2 (0.8)
Median (min, max)	0.0 (0, 0)	3.0 (0, 3)	2.0 (0, 2)	2.0 (0, 3)
Total amount of active study drug (mg)				
N	301	293	298	591
Mean (SD)	17.0 (2.8)	47.6 (6.6)	53.4 (8.5)	50.5 (8.2)
Median (min, max)	18.0 (2, 18)	48.0 (8, 64)	56.0 (8, 64)	48.0 (8, 64)
Duration of treatment (weeks)				
N	301	293	298	591
Mean (SD)	34.78 (5.20)	35.23 (4.18)	34.32 (5.87)	34.77 (5.12)
Median (min, max)	36.00 (4.0, 39.1)	36.00 (4.0, 42.1)	36.00 (4.0, 38.0)	36.00 (4.0, 42.1)

Duration (weeks) = [(date of last study intervention prior to Week 36) – (date of first study intervention) +28]/7; 28 days were added because of the minimum 4-week dosing interval in the study. Study interventions given at Week 36 or beyond are not included in this table.
See Definition of terms for treatment group description.

Table 91: Exposure to intervention in study eye: through week 36 (safety analysis set, only participants considered as completers for week 36)

	8q8/3 N=278 (100%)	8q8/5 N=273 (100%)	All 8mg N=551 (100%)
Participants with q8 or longer dosing interval through Week 36 [a]	246 (88.5%)	255 (93.4%)	501 (90.9%)
Participants with q12 as the last intended dosing interval [b]	192 (69.1%)		
Participants shortened to q4 dosing interval anytime	32 (11.5%)	18 (6.6%)	50 (9.1%)
Participants shortening dosing interval at W16	17 (6.1%)		
Participants shortening dosing interval at W24	10 (3.6%)	13 (4.8%)	23 (4.2%)
Participants shortening dosing interval at W32	5 (1.8%)	5 (1.8%)	10 (1.8%)

Only participants that did not discontinue study intervention prior to Week 36 are included.
(a) All participants on q8 interval for whom it was not planned to have their interval shortened (according to DRM criteria until W32) prior to Week 36
(b) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 36.

The mean number of active injections through Week 64 in the SAF population was 11.2, 8.2 and 8.8 in the 2q4, 8q8/3 and 8q8/5 treatment groups, respectively. For those 525 participants completing the Week 64 treatment period (Week 64 completers), the mean number of active injections was 11.7, 8.4 and 9.4 in the 2q4, 8q8/3 and 8q8/5 treatment groups, respectively. (Table 88)

Among the Week 64 completers (Table 89), the target dosing interval of ≥Q8 was maintained through Week 64 in 89.5% of participants in the All 8 mg group. From Week 32 for the 2q4 and 8q8/3 groups and from Week 40 for the 8q8/5 group, the participants meeting DRM criteria could have their dosing intervals extended by 4 weeks. Through Week 64, the last completed interval was Q12 for 67.8% and 78.5% of participants in the 2q4 and 8q8/5 groups, respectively. In the 8q8/3 group 81.4% had a last completed interval ≥Q12 with 56.1% of them at Q16. The last intended interval was Q16 in 50.0% and 62.1% in the 2q4 and 8q8/5 groups, respectively, and ≥Q16 in 64.3%in the 8q8/3 group with 40.5% assigned Q20 at Week 64. Fewer participants in the All 8 mg group vs the 2q4 group had a last completed dosing interval of Q4 (4.2% vs 13%, respectively).

Table 92: Exposure to study intervention in the study eye through week 64 (safety analysis set)

			2q4 N = 301 (100%)	8q8/3 N = 293 (100%)	8q8/5 N = 298 (100%)	All 8 mg N = 591 (100%)
Total number of injections, n	Active		3372	2388	2635	5023
	Sham		1076	2005	1659	3664
Number of active injections, n (%)		1	2 (0.7%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
		2	2 (0.7%)	1 (0.3%)	5 (1.7%)	6 (1.0%)
		3	6 (2.0%)	3 (1.0%)	4 (1.3%)	7 (1.2%)
		4	1 (0.3%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
		5	3 (1.0%)	5 (1.7%)	10 (3.4%)	15 (2.5%)
		6	4 (1.3%)	5 (1.7%)	3 (1.0%)	8 (1.4%)
		7	1 (0.3%)	11 (3.8%)	7 (2.3%)	18 (3.0%)
		8	1 (0.3%)	205 (70.0%)	20 (6.7%)	225 (38.1%)
		9	6 (2.0%)	28 (9.6%)	171 (57.4%)	199 (33.7%)
		10	18 (6.0%)	9 (3.1%)	52 (17.4%)	61 (10.3%)
		11	150 (49.8%)	8 (2.7%)	8 (2.7%)	16 (2.7%)
		12	52 (17.3%)	5 (1.7%)	8 (2.7%)	13 (2.2%)
		13	23 (7.6%)	3 (1.0%)	2 (0.7%)	5 (0.8%)
		14	9 (3.0%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
		15	11 (3.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
		16	12 (4.0%)	0	0	0
Number of active injections	n		301	293	298	591
	Mean (SD)		11.2 (2.4)	8.2 (1.7)	8.8 (1.9)	8.5 (1.8)
	Median (min, max)		11.0 (1, 16)	8.0 (1, 15)	9.0 (1, 15)	9.0 (1, 15)
Total amount of active study drug (mg)	n		301	293	298	591
	Mean (SD)		22.4 (4.9)	65.1 (13.4)	70.7 (15.4)	67.9 (14.7)
	Median (min, max)		22.0 (2, 32)	64.0 (8, 120)	72.0 (8, 120)	72.0 (8, 120)
Duration of treatment (weeks)	n		301	293	298	591
	Mean (SD)		60.58 (11.70)	61.34 (10.45)	58.93 (13.88)	60.13 (12.35)
	Median (min, max)		64.00 (4.0, 68.0)	64.00 (4.0, 68.0)	64.00 (4.0, 66.9)	64.00 (4.0, 68.0)

Duration (weeks) = [(date of last study intervention prior to Week 64) – (date of first study intervention) +28]/7; 28 days were added because of the minimum 4-week dosing interval in the study.
See Definition of terms for treatment group description.

Table 93: Proportion of participants with specific treatment intervals through week 64 (safety analysis set; only week 64 completers)

Number (%) of participants with the specified dosing		2q4 N = 270 (100%)	8q8/3 N = 269 (100%)	8q8/5 N = 256 (100%)	All 8 mg N = 525 (100%)
≥Q8 dosing interval from Week 32 through Week 64 [a]		189 (70.0%)			
≥Q8 dosing interval through Week 64 [b]			237 (88.1%)	233 (91.0%)	470 (89.5%)
Shortened to Q4 dosing interval anytime [c]		21 (7.8%)	32 (11.9%)	23 (9.0%)	55 (10.5%)
Extended dosing interval anytime [d]		252 (93.3%)	245 (91.1%)	232 (90.6%)	477 (90.9%)
Never extended dosing interval [e]		18 (6.7%)	24 (8.9%)	24 (9.4%)	48 (9.1%)
Last *intended* dosing interval [f]	Q4	21 (7.8%)	11 (4.1%)	10 (3.9%)	21 (4.0%)
	≥Q8	249 (92.2%)	258 (95.9%)	246 (96.1%)	504 (96.0%)
	≥Q12	210 (77.8%)	232 (86.2%)	219 (85.5%)	451 (85.9%)
	≥Q16	135 (50.0%)	173 (64.3%)	159 (62.1%)	332 (63.2%)
	Q20		109 (40.5%)		
Last *completed* dosing interval	Q4	35 (13.0%)	13 (4.8%)	9 (3.5%)	22 (4.2%)
	≥Q8	235 (87.0%)	256 (95.2%)	247 (96.5%)	503 (95.8%)
	≥Q12	183 (67.8%)	219 (81.4%)	201 (78.5%)	420 (80.0%)
	Q16		151 (56.1%)		

DRM = dose regimen modification; Q4 =every 4 weeks; Q8 = every 8 weeks; Q12 = every 12 weeks; Q16 = every 16 weeks; Q20 = every 20 weeks

Duration (weeks) = [(date of last study intervention prior to Week 36) - (date of first study intervention) +28]/7; 28 days were added because of the minimum 4-week dosing interval in the study. Only participants that did not discontinue study intervention prior to Week 64 are included (Week 64 completers).

(a) All participants on 2q4 extended to 8-week interval at the W32 visit for whom it was not planned to have their interval shortened to 4-week interval (according to DRM criteria until Week 60) prior to Week 64.

(b) All participants on 8q8 with 8-week or longer interval for whom it was not planned to have their interval shortened to 4-week interval (according to DRM criteria until Week 60) prior to Week 64.

(c) For 2q4 this includes participants that were extended to q8 dosing interval and subsequently shortened back to q4.

(d) All participants for whom it was planned to have their interval extended (according to DRM criteria until Week 60) prior to Week 64.

(e) All participants for whom it was not planned to have their interval extended (according to DRM criteria until Week 60) prior to Week 64.

(f) Based on DRM criteria assessed at the last visit with active injection before Week 64.

See Definition of terms for treatment group description.

Exposure in the fellow eye

From baseline through Week 36, few participants reported fellow-eye injections (either aflibercept 2mg or any locally approved treatment option), with frequencies slightly higher in the 2q4 group (3.0%) than in the All 8 mg group (1.7%); the mean (SD) number of injections was 3.7 (1.9), 3.4 (2.8) and 4.8 (2.3) in the 2q4, 8q8/3 and 8q8/5 groups, respectively. The numerical difference is not considered as clinically relevant.

In QUASAR, 93.7% of the patient completed the study through Q36 with more than 90% in all groups (95.0% in 2q4; 94.6% in 8q8/3 and 91.6% in 8q8/5). The primary reasons for discontinuation were withdrawal by subject (2.6% in 2q4, 2.7% in 8q8/3 and 5.4% in 8q8/5), death (0.7% in 2q4 and 8q8/3 and 1.0% in 8q8/5) and lost to follow-up (0.7% in all arms).

Up to week 64, comparable proportions of patients completed week 64 (89.4% in 2q4 arm and 88.8% in all 8 mg) with the most reported reason for discontinuation being withdrawal by subject (2.6% in 2q4 and 3.6% in all 8 mg).

Up to week 36, the mean number of active injections in the study eye was 8.5, 6.0 and 6.7 injections in the 2q4, 8q8/3 and 8q8/5 treatment groups, respectively. The mean total amount of active study (mg) was 17.0, 47,6 and 53,4 mg in the 2q4, 8q8/3 and 8q8/5 treatment groups, respectively. Through Week 36, the target dosing interval of Q8 was maintained in more than 90,9% in all 8mg group and in 88,5% for 2q4. The proportions of patient who shortened to q4 dosing interval at any time was low 11.5% in 2q4, 6.6% in 8q8/3 and 9.1% in 8q8/5.

Up to week 64, the mean number of active injections was 11.2, 8.2 and 8.8 in the 2q4, 8q8/3 and 8q8/5 treatment groups, respectively and the target dosing interval of ≥Q8 was maintained through Week 64

in 89.5% of participants in the All 8 mg group. In the All 8 mg group 4.2% vs 13% of the participants in the 2q4 group had a last completed dosing interval of Q4.

In the fellow eye, the mean number of injections was 3.7, 3.4 and 4.8 in the 2q4, 8q8/3 and 8q8/5 groups, respectively up to week 36.

- ***Demographic and other characteristics of study population***

For demographic and other characteristics of study population please refer to the *Efficacy section*.

Adverse events

- ***Analysis of adverse events***

    - **Overview of adverse events**

The overall incidences of TEAEs reported up to Week 36 were generally balanced between the All 8mg group and the 2q4 group; however, the incidence of ocular TEAEs in the study eye was slightly higher in the 8q8/3 group (35.2%) compared to the 8q8/5 group (28.9%) or the 2q4 group (28.2%) while the incidence of non-ocular TEAEs was slightly lower in the 8q8/3 group (47.1%) compared to the 8q8/5 group (51.0%) or the 2q4 group (50.2%).

Similar tendencies were observed up to week 64, for ocular TEAEs (8q8/3 group (50.5%) compared to the 8q8/5 group (44.3%) or the 2q4 group (47.2%)) and non-ocular TEAEs (68 (62.3%) participants in the All 8mg group (181 [61.8%] in the 8q8/3 group and 187 [62.8%] in the 8q8/5 group) and 189 (62.8%) participants in the 2q4 group).

Up to week 36, ocular TEAEs in the study eye that resulted in discontinuation of the study intervention affected few participants: 1 (0.3%) participant each in the 8q8/5 group and the 2q4 group, and no participants in the 8q8/3 group. Non-ocular TEAEs resulted in discontinuation of the study intervention in few participants: 5 (0.8%) participants in the All 8mg groups and 3 (1.0%) participants in the 2q4 group.

Up to week 64, 1 additional participant in the 8q8/5 group presented an ocular TEAE which lead to study discontinuation. Non-ocular TEAEs resulted in discontinuation of the study intervention in few participants: 7 (1.2%) participants in the All 8mg groups and 4 (1.0%) participants in the 2q4 group.

A total of 7 deaths were reported in this study, evenly distributed across the treatment groups, and all were associated with an SAE. None of the underlying SAEs were assessed as related to the study intervention or study procedure. No additional death was reported between week 36 and 64.

The incidences of ocular serious TEAEs in the study eye and non-ocular serious TEAEs were low and similar across the treatment groups. Most of the serious TEAEs were reported in single participants only.

The incidences of ocular TEAEs in the study eye and non-ocular TEAEs that were assessed to be related to the study intervention, IVT injection, and protocol required procedures were low and mostly reported for single participants only.

The results of the subgroup analyses of ocular TEAEs in the study eye and non-ocular TEAEs by different RVO types (CRVO/HRVO vs. BRVO) did not suggest clinically relevant differences between the treatment groups up to week 36 and 64.

Table 94: Adverse events: overall summary (safety analysis set)-Up to week 36

	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with adverse events				
Any AE	206 (68.4%)	200 (68.3%)	203 (68.1%)	403 (68.2%)
Any pre-treatment AE	25 (8.3%)	28 (9.6%)	30 (10.1%)	58 (9.8%)
Any TEAE	201 (66.8%)	196 (66.9%)	190 (63.8%)	386 (65.3%)
Any post-treatment AE	1 (0.3%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Any ocular TEAE	98 (32.6%)	117 (39.9%)	97 (32.6%)	214 (36.2%)
Study eye	85 (28.2%)	103 (35.2%)	86 (28.9%)	189 (32.0%)
Fellow eye	47 (15.6%)	49 (16.7%)	41 (13.8%)	90 (15.2%)
Any non-ocular TEAE	151 (50.2%)	138 (47.1%)	152 (51.0%)	290 (49.1%)
Any intervention-related TEAE	7 (2.3%)	14 (4.8%)	7 (2.3%)	21 (3.6%)
Any ocular intervention-related TEAE	6 (2.0%)	12 (4.1%)	6 (2.0%)	18 (3.0%)
Study eye	6 (2.0%)	12 (4.1%)	6 (2.0%)	18 (3.0%)
Fellow eye	0	0	0	0
Any non-ocular intervention-related TEAE	1 (0.3%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Any TEAE related to injection procedure	20 (6.6%)	38 (13.0%)	25 (8.4%)	63 (10.7%)
Any ocular TEAE related to injection procedure	19 (6.3%)	38 (13.0%)	25 (8.4%)	63 (10.7%)
Study eye	19 (6.3%)	38 (13.0%)	25 (8.4%)	63 (10.7%)
Fellow eye	0	1 (0.3%)	0	1 (0.2%)
Any non-ocular TEAE related to injection procedure	1 (0.3%)	0	0	0
Any TEAE related to protocol-required procedure	6 (2.0%)	9 (3.1%)	11 (3.7%)	20 (3.4%)
Any ocular TEAE related to protocol-required procedure	3 (1.0%)	5 (1.7%)	6 (2.0%)	11 (1.9%)
Study eye	3 (1.0%)	5 (1.7%)	6 (2.0%)	11 (1.9%)
Fellow eye	0	0	0	0
Any non-ocular TEAE related to protocol-required procedure	3 (1.0%)	4 (1.4%)	5 (1.7%)	9 (1.5%)
Any TEAE related to commercial aflibercept 2mg (of fellow eye)	0	0	0	0
Any TEAE leading to discontinuation of intervention	4 (1.3%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Any ocular TEAE leading to discontinuation of intervention	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Study eye	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Fellow eye	0	0	0	0
Any non-ocular TEAE leading to discontinuation of intervention	3 (1.0%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Any TEAE related to medical device	0	1 (0.3%)	0	1 (0.2%)
Any ocular TEAE related to medical device	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 non-ocular TEAE related to medical device	0	0	0	0
Any TEAE of special interest	9 (3.0%)	1 (0.3%)	5 (1.7%)	6 (1.0%)
Any TEAE of APTC events	5 (1.7%)	0	3 (1.0%)	3 (0.5%)
Any TEAE of hypertension	14 (4.7%)	24 (8.2%)	24 (8.1%)	48 (8.1%)
Any TEAE of intraocular inflammation of study eye	4 (1.3%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Any TEAE of nasal mucosal finding	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Maximum intensity for any ocular TEAE				
Study eye				
Mild	58 (19.3%)	76 (25.9%)	66 (22.1%)	142 (24.0%)
Moderate	21 (7.0%)	25 (8.5%)	17 (5.7%)	42 (7.1%)
Severe	6 (2.0%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Fellow eye				
Mild	33 (11.0%)	35 (11.9%)	34 (11.4%)	69 (11.7%)
Moderate	14 (4.7%)	13 (4.4%)	7 (2.3%)	20 (3.4%)
Severe	0	1 (0.3%)	0	1 (0.2%)

Maximum intensity for any non-ocular TEAE				
Mild	84 (27.9%)	86 (29.4%)	95 (31.9%)	181 (30.6%)
Moderate	51 (16.9%)	38 (13.0%)	45 (15.1%)	83 (14.0%)
Severe	16 (5.3%)	14 (4.8%)	12 (4.0%)	26 (4.4%)
Any SAE	34 (11.3%)	25 (8.5%)	32 (10.7%)	57 (9.6%)
Any pre-treatment SAE	2 (0.7%)	0	5 (1.7%)	5 (0.8%)
Any TESAE	32 (10.6%)	24 (8.2%)	26 (8.7%)	50 (8.5%)
Any post-treatment SAE	1 (0.3%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Any ocular SAE	8 (2.7%)	4 (1.4%)	4 (1.3%)	8 (1.4%)
Study eye	8 (2.7%)	3 (1.0%)	4 (1.3%)	7 (1.2%)
Fellow eye	0	1 (0.3%)	0	1 (0.2%)
Any non-ocular SAE	26 (8.6%)	22 (7.5%)	28 (9.4%)	50 (8.5%)
Any ocular TESAE	7 (2.3%)	4 (1.4%)	4 (1.3%)	8 (1.4%)
Study eye	7 (2.3%)	3 (1.0%)	4 (1.3%)	7 (1.2%)
Fellow eye	0	1 (0.3%)	0	1 (0.2%)
Any non-ocular TESAE	25 (8.3%)	21 (7.2%)	22 (7.4%)	43 (7.3%)
Any intervention-related TESAE	2 (0.7%)	0	1 (0.3%)	1 (0.2%)
Any ocular intervention-related TESAE	2 (0.7%)	0	1 (0.3%)	1 (0.2%)
Study eye	2 (0.7%)	0	1 (0.3%)	1 (0.2%)
Fellow eye	0	0	0	0
Any non-ocular intervention-related TESAE	0	0	0	0
Any TESAE related to protocol-required procedure	0	0	0	0
Any TESAE related to commercial aflibercept 2mg (of fellow eye)	0	0	0	0
Any TESAE related to medical device	0	0	0	0
Any TESAE of special interest	6 (2.0%)	1 (0.3%)	4 (1.3%)	5 (0.8%)
Any TESAE of APTC events	4 (1.3%)	0	3 (1.0%)	3 (0.5%)
Any TESAE of hypertension	1 (0.3%)	0	0	0
Any TESAE of intraocular inflammation of study eye	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Any TESAE of nasal mucosal finding	1 (0.3%)	0	0	0
Maximum intensity for any ocular TESAE				
Study eye				
Mild	0	0	1 (0.3%)	1 (0.2%)
Moderate	4 (1.3%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Severe	3 (1.0%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Fellow eye				
Severe	0	1 (0.3%)	0	1 (0.2%)
Maximum intensity for any non-ocular TESAE				
Mild	1 (0.3%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Moderate	10 (3.3%)	8 (2.7%)	9 (3.0%)	17 (2.9%)
Severe	14 (4.7%)	11 (3.8%)	10 (3.4%)	21 (3.6%)
Total number of deaths	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Any AE with outcome death	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Any pre-treatment AE with outcome death	0	0	0	0
Any TEAE with outcome death	2 (0.7%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Any post-treatment AE with outcome death	0	0	1 (0.3%)	1 (0.2%)
Deaths not attributed to an AE	0	0	0	0

AE = Adverse event; APTC = Anti-platelet trialists' collaboration; RVO = Retinal vein occlusion; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event; TESAE = Treatment-emergent serious adverse event
Pre-treatment adverse events are defined as AEs that start before first administration of study intervention.
TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days. For the participants who have not discontinued study treatment prematurely (i.e., are 'ongoing') at the Week 36 analysis, all AEs that started at first injection or later will be considered treatment-emergent.
Post-treatment adverse events are defined as AEs that start more than 30 days after the stop of study intervention.
Only the most severe intensity is counted for multiple occurrences of the same AE in one individual. 'Missing' is considered to be the lowest category of intensity.
Adverse Event of Special Interest (AESI) are arterial thromboembolic events including cerebrovascular ischemic events and cardiovascular ischemic events.

Table 95: Adverse events: overall summary (safety analysis set)-Up to week 64

Number (%) of participants with specified events	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Any AE	244 (81.1%)	235 (80.2%)	233 (78.2%)	468 (79.2%)
Any pre-treatment AE	25 (8.3%)	29 (9.9%)	33 (11.1%)	62 (10.5%)
Any TEAE	236 (78.4%)	230 (78.5%)	225 (75.5%)	455 (77.0%)
Any post-treatment AE	18 (6.0%)	11 (3.8%)	10 (3.4%)	21 (3.6%)
Any ocular TEAE in the study eye	127 (42.2%)	134 (45.7%)	118 (39.6%)	252 (42.6%)
Any non-ocular TEAE	189 (62.8%)	181 (61.8%)	187 (62.8%)	368 (62.3%)
Any ocular intervention-related TEAE in the study eye	6 (2.0%)	14 (4.8%)	8 (2.7%)	22 (3.7%)
Any non-ocular intervention-related TEAE	2 (0.7%)	3 (1.0%)	2 (0.7%)	5 (0.8%)
Any ocular TEAE in study eye leading to discontinuation of intervention	1 (0.3%)	0	2 (0.7%)	2 (0.3%)
Any non-ocular TEAE leading to discontinuation of intervention	4 (1.3%)	3 (1.0%)	4 (1.3%)	7 (1.2%)
Any TEAE of special interest (AESI of ATE)	9 (3.0%)	2 (0.7%)	8 (2.7%)	10 (1.7%)
Any TEAE of APTC events	6 (2.0%)	2 (0.7%)	7 (2.3%)	9 (1.5%)
Any TEAE of hypertension	21 (7.0%)	38 (13.0%)	29 (9.7%)	67 (11.3%)
Any TEAE of intraocular inflammation of study eye	5 (1.7%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Any TEAE of nasal mucosal finding	2 (0.7%)	3 (1.0%)	1 (0.3%)	4 (0.7%)
Maximum intensity for any ocular TEAE in the study eye				
Mild	83 (27.6%)	89 (30.4%)	91 (30.5%)	180 (30.5%)
Moderate	38 (12.6%)	43 (14.7%)	23 (7.7%)	66 (11.2%)
Severe	6 (2.0%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Maximum intensity for any non-ocular TEAE				
Mild	102 (33.9%)	105 (35.8%)	109 (36.6%)	214 (36.2%)
Moderate	65 (21.6%)	56 (19.1%)	60 (20.1%)	116 (19.6%)
Severe	22 (7.3%)	20 (6.8%)	18 (6.0%)	38 (6.4%)
Any SAE	49 (16.3%)	39 (13.3%)	45 (15.1%)	84 (14.2%)
Any pre-treatment SAE	2 (0.7%)	0	5 (1.7%)	5 (0.8%)
Any TESAE	44 (14.6%)	37 (12.6%)	38 (12.8%)	75 (12.7%)
Any post-treatment SAE	7 (2.3%)	3 (1.0%)	3 (1.0%)	6 (1.0%)
Any ocular SAE in the study eye	10 (3.3%)	6 (2.0%)	5 (1.7%)	11 (1.9%)
Any non-ocular SAE	39 (13.0%)	34 (11.6%)	40 (13.4%)	74 (12.5%)
Any ocular TESAE in the study eye	8 (2.7%)	5 (1.7%)	5 (1.7%)	10 (1.7%)
Any non-ocular TESAE	36 (12.0%)	33 (11.3%)	33 (11.1%)	66 (11.2%)
Any TESAE of special interest	6 (2.0%)	1 (0.3%)	6 (2.0%)	7 (1.2%)
Any TESAE of APTC events	4 (1.3%)	1 (0.3%)	6 (2.0%)	7 (1.2%)
Any TESAE of hypertension	2 (0.7%)	0	0	0
Any TESAE of intraocular inflammation of study eye	3 (1.0%)	2 (0.7%)	0	2 (0.3%)
Any TESAE of nasal mucosal finding	1 (0.3%)	0	0	0
Maximum intensity for any ocular TESAE in the study eye				
Mild	0	0	1 (0.3%)	1 (0.2%)
Moderate	4 (1.3%)	3 (1.0%)	2 (0.7%)	5 (0.8%)
Severe	4 (1.3%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Maximum intensity for any non-ocular TESAE				
Mild	3 (1.0%)	4 (1.4%)	4 (1.3%)	8 (1.4%)
Moderate	14 (4.7%)	15 (5.1%)	13 (4.4%)	28 (4.7%)
Severe	19 (6.3%)	14 (4.8%)	16 (5.4%)	30 (5.1%)
Total number of deaths	3 (1.0%)	2 (0.7%)	5 (1.7%)	7 (1.2%)
Any AE with outcome death	3 (1.0%)	2 (0.7%)	5 (1.7%)	7 (1.2%)
Any pre-treatment AE with outcome death	0	0	0	0
Any TEAE with outcome death	3 (1.0%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Any post-treatment AE with outcome death	0	0	2 (0.7%)	2 (0.3%)

AE = Adverse event; APTC = Anti-platelet trialists' collaboration; RVO = Retinal vein occlusion; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event; TESAE = Treatment-emergent serious adverse event

Pre-treatment adverse events are defined as AEs that start before first administration of study intervention.
TEAEs are defined as AEs that started in the time frame from first injection to the last injection (active or sham) in the study plus 30 days.

Post-treatment adverse events are defined as AEs that start more than 30 days after the stop of study intervention.
Only the most severe intensity is counted for multiple occurrences of the same AE in one individual. 'Missing' is considered to be the lowest category of intensity.

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

Up to week 36, ocular TEAEs in the study eye were reported in slightly higher proportion in 8q8/3 (35.5%) compared to 2q4 (28.2%) and 8q8/5 (28.9%). Ocular TEAEs related to the study intervention in the study eye were reported in a higher proportion in 8q8/3 (4.1%) while similar for 2q4 and 8q8/5 (2.0%). Ocular TEAEs related to the injection procedure in the study eye were higher in 8q8/3 arm (13.0%) compared to 8q8/5 (8.4%) and 2q4 (6.3%). Ocular TEAEs related to protocol-required procedure in the study eye were low and slightly higher in all 8 mg (1.9% vs 1.0% in 2q4). No TEAEs

were assessed as related to aflibercept 2 mg in the fellow eye. One TEAE assessed as related to injection procedure occurred in the fellow eye in the 8q8/3 group. Ocular TEAEs leading to treatment discontinuation were low and comparable (1.3% in 2q4 and 1.0% in all 8 mg group). Serious ocular TEAEs in the study eye were low and higher in 2q4 (2.3% vs 1.2% in all 8 mg group). Serious ocular TEAEs in the study eye related to study intervention (0.7% in 2q4 and 0.3% in 8q8/5) and injection-procedure (1.3% in 2q4 and 0.3% in 8q8/3 and 8q8/5) were low. TEAEs of intraocular inflammation in the study eye occurred in slightly higher proportion in 2q4 (1.3% compared to 0.3% in 8q8/5 and 0.7% in 8q8/3).

Up to week 64, comparable proportions of patients in QUASAR presented at least one TEAEs, 77.0% and 78.4% in all 8 mg group and 2q4 group respectively. Ocular TEAEs in the study eye were reported in similar proportions between all 8 mg (42.6%) and 2q4 arm (42.2%). Severe ocular TEAEs in the study eye occurred in low proportions (2.0% in 2q4 arm and 1.0% in all 8 mg). Ocular SAE in the study eye occurred in low proportions, 3.3% participants in 2q4 arm and 1.9% in all 8 mg group. Ocular TEAEs in the study eye assessed as related to study intervention were slightly more reported in all 8 mg arm (3.7% vs 2.0% in 2q4 arm). Incidence of ocular TEAEs leading to study discontinuation were low in both groups (0.3%).

Non-ocular TEAEs were reported in slightly lower proportions in 8q8/3 arm (47.1%) while being comparable between All 8 mg group (49.1%) and 2q4 (50.2%). Non-ocular TEAEs assessed as related to study intervention were low (0.3% in 2q4 and 0.5% in all 8 mg). Non-ocular TEAEs related to injection procedure occurred in one patient in 2q4. Non-ocular TEAE related to protocol required procedure were reported in comparable proportions (1.0% in 2q4 and 1.5% in all 8 mg group). Non-ocular TEAEs leading to study intervention discontinuation were low and comparable (1.0% in 2q4 and 0,8% in all 8 mg group). Serious non-ocular TEAEs were comparable between treatment arms (8.3% in 2q4, 7.2% in 8q8/3 and 7.4% in 8q8/5 groups). No serious ocular TEAEs were assessed as related to study intervention or injection procedure. TEAEs of APTC events occurred in 2q4 (1.7%) and 8q8/5 (1.0%). TEAEs of hypertension occurred more in all 8 mg group (8.1%) compared to 2q4 (4.7%).

Up to week 64, non-ocular TEAEs occurred in similar proportions in both arms (62.8% in 2q4 and 62.3% in all 8 mg). Severe non-ocular TEAEs occurred in low proportions in both treatment groups (7.3% in 2q4 arm and 6.4% in all 8 mg). Non-ocular SAEs were reported in similar proportions, 13.0% in 2q4 arm and 12.5% in all 8 mg arm. Non-ocular intervention-related TEAE were observed in low and comparable proportions 0.7% in 2q4 arm and 0.8% in all 8 mg group. Non-ocular TEAEs leading to study discontinuation remained in low and comparable proportions 1,3% in 2q4 arm, 1,0% in 8q8/3 and 1.3% in 8q8/5 arms.

TEAEs with the death outcome occurred in comparable proportions (0.7%) in all treatment arms up to week 36. Deaths were reported in 3 additional patients in 2q4 arm (1.0%) and 7 patients in all 8 mg arm (1.2%) up to week 64.

– Common adverse events

○ *Ocular TEAEs in the study eye*

Ocular TEAEs in the study eye were reported in 189 (32.0%) participants in the All 8mg group (103 [35.2%] in the 8q8/3 group and 86 [28.9%] in the 8q8/5 group) and 85 (28.2%) participants in the 2q4 group. The most frequently reported ocular TEAE in the study eye was IOP increased, which was reported in a numerically higher proportion of participants in the All 8 mg group (31 [5.2%] participants: 16 [5.5%] and 15 [5.0%] for the 8q8/3 and 8q8/5 groups, respectively) than in the 2q4 group (5 [1.7%] participants). None of the IOP increased events were serious or led to discontinuation of study intervention, most were mild or moderate in intensity and resolved without sequela. IOP increased was

assessed as not related to the study intervention in the majority of participants who experienced such events. Further discussion of IOP increased based on a predefined set of PTs is provided in Section 2.1.6.3. All other ocular TEAEs in the study eye were reported in <5% of participants in any treatment group (Table 92).

Table 96: Frequent ocular TEAEs in the study eye: (safety analysis set) 10 most frequent PTs in each treatment group with their associated SOCs

Primary System Organ Class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	85 (28.2%)	103 (35.2%)	86 (28.9%)	189 (32.0%)
Eye disorders	73 (24.3%)	90 (30.7%)	70 (23.5%)	160 (27.1%)
Cataract	9 (3.0%)	5 (1.7%)	10 (3.4%)	15 (2.5%)
Conjunctival haemorrhage	6 (2.0%)	10 (3.4%)	7 (2.3%)	17 (2.9%)
Dry eye	6 (2.0%)	4 (1.4%)	5 (1.7%)	9 (1.5%)
Epiretinal membrane	6 (2.0%)	3 (1.0%)	7 (2.3%)	10 (1.7%)
Punctate keratitis	5 (1.7%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Conjunctivitis allergic	4 (1.3%)	3 (1.0%)	2 (0.7%)	5 (0.8%)
Ocular hypertension	4 (1.3%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Visual acuity reduced	4 (1.3%)	12 (4.1%)	8 (2.7%)	20 (3.4%)
Eye pain	3 (1.0%)	5 (1.7%)	4 (1.3%)	9 (1.5%)
Vitreous floaters	3 (1.0%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Vitreous detachment	2 (0.7%)	8 (2.7%)	9 (3.0%)	17 (2.9%)
Glaucoma	0	4 (1.4%)	1 (0.3%)	5 (0.8%)
Macular thickening	0	5 (1.7%)	0	5 (0.8%)
Injury, poisoning and procedural complications	4 (1.3%)	8 (2.7%)	3 (1.0%)	11 (1.9%)
Intra-ocular injection complication	1 (0.3%)	5 (1.7%)	0	5 (0.8%)
Investigations	7 (2.3%)	17 (5.8%)	15 (5.0%)	32 (5.4%)
Intraocular pressure increased	5 (1.7%)	16 (5.5%)	15 (5.0%)	31 (5.2%)

Ocular TEAEs in the study eye were mostly mild or moderate in intensity. Severe ocular TEAEs in the study eye were reported in 5 (0.8%) participants in the All 8mg group (2 [0.7%] and 3 [1.0%] for the 8q8/3 and 8q8/5 groups, respectively) and 6 (2.0%) participants in the 2q4 group. All severe ocular TEAEs were reported in single participants except for Cataract (2 participants in the 8q8/5 group) (Table 93).

Table 97: All severe ocular TEAEs in the study eye (safety analysis set)

Primary System Organ Class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	6 (2.0%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Eye disorders	5 (1.7%)	0	3 (1.0%)	3 (0.5%)
Blindness	1 (0.3%)	0	0	0
Cataract	0	0	2 (0.7%)	2 (0.3%)
Macular hole	1 (0.3%)	0	0	0
Posterior capsule opacification	1 (0.3%)	0	0	0
Retinal artery occlusion	1 (0.3%)	0	0	0
Retinal detachment	1 (0.3%)	0	0	0
Retinal vein occlusion	0	0	1 (0.3%)	1 (0.2%)
Infections and infestations	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Endophthalmitis	0	1 (0.3%)	0	1 (0.2%)
Tooth abscess	1 (0.3%)	0	0	0
Investigations	0	1 (0.3%)	0	1 (0.2%)
Intraocular pressure increased	0	1 (0.3%)	0	1 (0.2%)

In general, no clinically meaningful differences were observed in type of TEAEs or their frequencies between the All 8mg and 2q4 groups, and reported events were consistent with the known safety profile of aflibercept. No clinically relevant differences were observed in the results of subgroup analysis of ocular TEAEs in the study eye by different RVO types (CRVO/HRVO vs. BRVO) even though numerical differences across the treatment groups were occasionally observed within either subgroup.

Up to week 64, Ocular TEAEs in the study eye were reported in 252 (42.6%) participants in the All 8mg group (134 [45.7%] in the 8q8/3 group and 118 [39.6%] in the 8q8/5 group) and 127 (42.2%) participants in the 2q4 group (Table 94). The most frequently reported ocular TEAE in the study eye was

Cataract, which was reported in 29 (4.9%) participants in the All 8 mg group (11 [3.8%] and 18 [6.0%] for the 8q8/3 and 8q8/5 groups, respectively) and 17 (5.6%) participants in the 2q4 group; followed by IOP increased which was reported in numerically higher proportion of participants in the All 8 mg group (35 [5.9%] participants: 19 [6.5%] and 16 [5.4%] for the 8q8/3 and 8q8/5 groups, respectively) than in the 2q4 group (8 [2.7%] participants). None of the IOP increased events were serious or led to discontinuation of study intervention, most were mild or moderate in intensity and resolved without sequela. IOP increased was assessed as not related to the study intervention in the majority of participants who experienced such events. All other ocular TEAEs in the study eye were reported in ≤5.5% of participants in any treatment group. In general, no clinically meaningful differences were observed in type of TEAEs or their frequencies between the All 8mg and 2q4 groups, and reported events were consistent with the known safety profile of aflibercept.

Table 98: Number (%) of participants with ocular TEAEs in the study eye: 10 most frequent PTs in each treatment group with their associated SOCs: (safety analysis set)

Primary System Organ Class Preferred term MedDRA version 28.0	**2q4** N=301 (100%)	**8q8/3** N=293 (100%)	**8q8/5** N=298 (100%)	**All 8 mg** N=591 (100%)
Number (%) of participants with at least one such adverse event	**127 (42.2%)**	**134 (45.7%)**	**118 (39.6%)**	**252 (42.6%)**
Eye disorders	112 (37.2%)	118 (40.3%)	102 (34.2%)	220 (37.2%)
Cataract	17 (5.6%)	11 (3.8%)	18 (6.0%)	29 (4.9%)
Visual acuity reduced	12 (4.0%)	16 (5.5%)	9 (3.0%)	25 (4.2%)
Dry eye	9 (3.0%)	4 (1.4%)	9 (3.0%)	13 (2.2%)
Conjunctival haemorrhage	8 (2.7%)	14 (4.8%)	12 (4.0%)	26 (4.4%)
Macular thickening	8 (2.7%)	12 (4.1%)	1 (0.3%)	13 (2.2%)
Punctate keratitis	7 (2.3%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Epiretinal membrane	6 (2.0%)	6 (2.0%)	10 (3.4%)	16 (2.7%)
Macular oedema	6 (2.0%)	10 (3.4%)	5 (1.7%)	15 (2.5%)
Conjunctivitis allergic	5 (1.7%)	4 (1.4%)	3 (1.0%)	7 (1.2%)
Ocular hypertension	5 (1.7%)	5 (1.7%)	3 (1.0%)	8 (1.4%)
Vitreous detachment	4 (1.3%)	9 (3.1%)	10 (3.4%)	19 (3.2%)
Vitreous floaters	4 (1.3%)	6 (2.0%)	3 (1.0%)	9 (1.5%)
Eye pain	3 (1.0%)	5 (1.7%)	4 (1.3%)	9 (1.5%)
Glaucoma	1 (0.3%)	5 (1.7%)	2 (0.7%)	7 (1.2%)
Injury, poisoning and procedural complications	6 (2.0%)	10 (3.4%)	7 (2.3%)	17 (2.9%)
Intra-ocular injection complication	1 (0.3%)	5 (1.7%)	0	5 (0.8%)
Investigations	11 (3.7%)	20 (6.8%)	16 (5.4%)	36 (6.1%)
Intraocular pressure increased	8 (2.7%)	19 (6.5%)	16 (5.4%)	35 (5.9%)

The results of the subgroup analyses by RVO types (CRVO/HRVO and BRVO) for ocular TEAEs in the study eye show slightly higher incidences in the CRVO/HRVO subgroup due to a numerically higher proportion of participants reporting Epiretinal membrane and Visual acuity reduced compared to the BRVO subgroup. In addition, a few more events were reported in the CRVO/HRVO subgroup under the SOC Eye disorders, but most of them were infrequently reported (<8% of participants in any treatment group). Overall, no clinically relevant differences were observed within either subgroup, although numerical differences across the treatment groups were occasionally observed.

The most frequently reported ocular TEAEs in the study eye were IOP increased (5.2% in all 8 mg group vs 1.7% in 2q4 group), Visual acuity reduced (4.1% in 8q8/3, 2.7% in 8q8/5 and 1.3% in 2q8), Cataract (1.7% in 8q8/3, 3.4% in 8q8/5 and 3.0% in 2q8), Vitreous detachment (2.7% in 8q8/3, 3.0% in 8q8/5 and 0.7% in 2q8) and Conjunctival haemorrhage (3.4% in 8q8/3, 2.3 % in 8q8/5 and 2.0% in 2q8).

Ocular TEAEs in the study eye were mainly mild (19.3% in 2q4 and 24.0% in all 8 mg group) to moderate (7.0% in 2q4 and 7.1% in all 8 mg group) in intensity. Severe ocular TEAEs in the study eye were reported in low proportions (2.0% in 2q4, 0.7% in 8q8/3 and 1.0% in 8q8/5). All these events occurred in single participants, apart from cataract in 2 participants in 8q8/5 and consisted of:

-in 2q4: Blindness (recovered/resolved, not related, not serious, drug interrupted), Macular hole (not recovered/not resolved, related to injection procedure, serious, drug withdrawn), Posterior capsule opacification (recovered/resolved with surgical procedure capsulotomy, not related, not serious, dose not changed), Retinal artery occlusion (not recovered/not resolved, not related, serious, dose not changed) and Retinal detachment (recovering/resolving, related to injection procedure, serious, drug interrupted);

- in 8q8/3: Endophthalmitis (recovered/resolved with sequelae, not related, serious, dose not changed) and IOP increased (two events occurred in one patient in both the study eye and fellow eye at 2 weeks of interval, recovering/resolving, not related, not serious, drug interrupted after the second event)

-in 8q8/5: Cataract (in one patient recovered/resolved with sequelae, related to injection procedure, serious, drug interrupted and in the other patient recovering/resolving, not related, not serious, drug not changed) and Retinal vein occlusion (recovered/resolved, not related, not serious, dose not changed)

Up to week 64, similar to week 36, the most reported ocular TEAEs in the study eye were IOP (2.7% in 2q4 arm and 5.9% in all 8 mg arm), Cataract (5.6% in 2q4 arm and 4.9% in all 8 mg arm) and Visual acuity reduced (4.0% in 2q4 arm and 5.5% in all 8 mg arm). Subgroup analyses by RVO types in the study eye show slightly higher incidences in the CRVO/HRVO subgroup or epiretinal membrane and visual acuity reduced compared to the BRVO subgroup.

- ***Ocular TEAEs in the fellow eye***

Overall, ocular TEAEs in the fellow eye were reported in 90 (15.2%) participants in the All 8mg group (49 [16.7%] in the 8q8/3 group and 41 [13.8%] in the 8q8/5 group) and 47 (15.6%) participants in the 2q4 group. The most frequently reported ocular TEAEs in the fellow eye were Cataract (11 [1.9%] participants in the All 8mg group and 9 [3.0%] in the 2q4 group). Ocular TEAEs in the fellow eye were reported infrequently for all other PTs and were generally balanced across the treatment groups.

- ***Non-ocular TEAEs***

Non-ocular TEAEs were reported in a similar proportion of participants in the All 8mg group and the 2q4 group. The majority of the TEAEs were in the SOC of Infections and infestations; however, the most common TEAE was Hypertension, which was reported in 6.6% of participants in the All 8mg group and 3.3% of participants in the 2q4 group. This is consistent with the imbalance in incidence of non-ocular medical history of the PT Hypertension with 61.9% in the All 8mg group compared to 57.5% in the 2q4 group. All cases of Hypertension were non-serious, assessed as not related to study intervention, almost all were mild or moderate intensity. Blood pressure changes from baseline and further discussion of Hypertension based on a predefined set of PTs are further in Section *Analysis of adverse events by organ system or syndrome*. No clinically relevant changes in BP measurements were observed and no relevant differences were seen across the treatment groups. All other non-ocular TEAEs were reported in <5.0% of participants in any treatment group, except Nasopharyngitis (5.1% in 8q8/3 group) (Table 95).

Table 99: Frequent non-ocular TEAEs (safety analysis set) 10 most frequent PTs in each treatment group with their associated SOCs

Primary System Organ Class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	151 (50.2%)	138 (47.1%)	152 (51.0%)	290 (49.1%)
Gastrointestinal disorders	21 (7.0%)	16 (5.5%)	18 (6.0%)	34 (5.8%)
Vomiting	5 (1.7%)	1 (0.3%)	0	1 (0.2%)
Nausea	4 (1.3%)	4 (1.4%)	3 (1.0%)	7 (1.2%)
General disorders and administration site conditions	11 (3.7%)	13 (4.4%)	8 (2.7%)	21 (3.6%)
Chest pain	2 (0.7%)	4 (1.4%)	1 (0.3%)	5 (0.8%)
Oedema peripheral	2 (0.7%)	4 (1.4%)	0	4 (0.7%)
Infections and infestations	58 (19.3%)	54 (18.4%)	57 (19.1%)	111 (18.8%)
Urinary tract infection	10 (3.3%)	4 (1.4%)	11 (3.7%)	15 (2.5%)
Nasopharyngitis	9 (3.0%)	15 (5.1%)	14 (4.7%)	29 (4.9%)
COVID-19	6 (2.0%)	13 (4.4%)	6 (2.0%)	19 (3.2%)
Influenza	6 (2.0%)	4 (1.4%)	1 (0.3%)	5 (0.8%)
Upper respiratory tract infection	5 (1.7%)	3 (1.0%)	3 (1.0%)	6 (1.0%)
Pharyngitis	0	4 (1.4%)	0	4 (0.7%)
Investigations	17 (5.6%)	19 (6.5%)	23 (7.7%)	42 (7.1%)
Blood pressure increased	2 (0.7%)	5 (1.7%)	2 (0.7%)	7 (1.2%)
Metabolism and nutrition disorders	24 (8.0%)	9 (3.1%)	22 (7.4%)	31 (5.2%)
Hyperlipidaemia	7 (2.3%)	1 (0.3%)	3 (1.0%)	4 (0.7%)
Hypercholesterolaemia	5 (1.7%)	3 (1.0%)	7 (2.3%)	10 (1.7%)
Type 2 diabetes mellitus	5 (1.7%)	0	4 (1.3%)	4 (0.7%)
Musculoskeletal and connective tissue disorders	24 (8.0%)	22 (7.5%)	17 (5.7%)	39 (6.6%)
Arthralgia	6 (2.0%)	3 (1.0%)	4 (1.3%)	7 (1.2%)
Nervous system disorders	19 (6.3%)	17 (5.8%)	19 (6.4%)	36 (6.1%)
Headache	5 (1.7%)	6 (2.0%)	6 (2.0%)	12 (2.0%)
Respiratory, thoracic and mediastinal disorders	13 (4.3%)	15 (5.1%)	8 (2.7%)	23 (3.9%)
Cough	4 (1.3%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Vascular disorders	16 (5.3%)	23 (7.8%)	26 (8.7%)	49 (8.3%)
Hypertension	10 (3.3%)	19 (6.5%)	20 (6.7%)	39 (6.6%)

Non-ocular TEAEs were mostly mild or moderate. Severe non-ocular TEAEs were reported in 26 (4.4%) participants in the All 8mg group (14 [4.8%] and 12 [4.0%] for the 8q8/3 and 8q8/5 groups, respectively) and 16 (5.3%) participants in the 2q4 group. All severe non-ocular TEAEs were reported in single participants except for Bradycardia and Sepsis (both in 2 participants in the 8q8/3 group), and Type 2 diabetes mellitus (2 participants in the 2q4 group) (Table 96).

Table 100: All severe non-ocular TEAEs (safety analysis set)

Primary System Organ Class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	16 (5.3%)	14 (4.8%)	12 (4.0%)	26 (4.4%)
Blood and lymphatic system disorders	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Blood loss anaemia	0	0	1 (0.3%)	1 (0.2%)
Pancytopenia	1 (0.3%)	0	0	0
Cardiac disorders	0	2 (0.7%)	1 (0.3%)	3 (0.5%)
Bradycardia	0	2 (0.7%)	0	2 (0.3%)
Coronary artery disease	0	1 (0.3%)	0	1 (0.2%)
Myocardial infarction	0	0	1 (0.3%)	1 (0.2%)
Gastrointestinal disorders	1 (0.3%)	3 (1.0%)	0	3 (0.5%)
Femoral hernia incarcerated	0	1 (0.3%)	0	1 (0.2%)
Hiatus hernia	0	1 (0.3%)	0	1 (0.2%)
Lower gastrointestinal haemorrhage	0	1 (0.3%)	0	1 (0.2%)
Small intestinal obstruction	1 (0.3%)	0	0	0
General disorders and administration site conditions	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Chest pain	0	1 (0.3%)	0	1 (0.2%)
Incarcerated hernia	1 (0.3%)	0	0	0
Hepatobiliary disorders	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cholecystitis acute	0	1 (0.3%)	0	1 (0.2%)

Primary System Organ Class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Cholecystitis chronic	0	0	1 (0.3%)	1 (0.2%)
Infections and infestations	2 (0.7%)	5 (1.7%)	2 (0.7%)	7 (1.2%)
Abdominal abscess	1 (0.3%)	0	0	0
Bronchitis	0	0	1 (0.3%)	1 (0.2%)
COVID-19	0	1 (0.3%)	0	1 (0.2%)
Diverticulitis	0	1 (0.3%)	0	1 (0.2%)
Gastroenteritis	0	1 (0.3%)	0	1 (0.2%)
Infectious pleural effusion	0	1 (0.3%)	0	1 (0.2%)
Pneumonia	1 (0.3%)	0	0	0
Pneumonia pseudomonal	0	0	1 (0.3%)	1 (0.2%)
Sepsis	0	2 (0.7%)	0	2 (0.3%)
Injury, poisoning and procedural complications	0	1 (0.3%)	2 (0.7%)	3 (0.5%)
Brain herniation	0	0	1 (0.3%)	1 (0.2%)
Procedural pain	0	0	1 (0.3%)	1 (0.2%)
Rib fracture	0	1 (0.3%)	0	1 (0.2%)
Subdural haematoma	0	0	1 (0.3%)	1 (0.2%)
Investigations	1 (0.3%)	0	0	0
Haemoglobin increased	1 (0.3%)	0	0	0
Metabolism and nutrition disorders	2 (0.7%)	0	0	0
Diabetic ketoacidosis	1 (0.3%)	0	0	0
Type 2 diabetes mellitus	2 (0.7%)	0	0	0
Musculoskeletal and connective tissue disorders	2 (0.7%)	1 (0.3%)	2 (0.7%)	3 (0.5%)
Arthralgia	0	0	1 (0.3%)	1 (0.2%)
Back pain	0	0	1 (0.3%)	1 (0.2%)
Intervertebral disc compression	1 (0.3%)	0	0	0
Myalgia	1 (0.3%)	0	0	0
Pain in extremity	0	1 (0.3%)	0	1 (0.2%)
Vertebral lateral recess stenosis	1 (0.3%)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7%)	1 (0.3%)	4 (1.3%)	5 (0.8%)
Colon cancer	0	0	1 (0.3%)	1 (0.2%)
Lung neoplasm malignant	0	0	1 (0.3%)	1 (0.2%)
Metastatic neoplasm	1 (0.3%)	0	0	0
Oesophageal carcinoma	0	1 (0.3%)	0	1 (0.2%)
Prostate cancer metastatic	0	0	1 (0.3%)	1 (0.2%)
Rectal cancer	0	0	1 (0.3%)	1 (0.2%)
Squamous cell carcinoma of lung	1 (0.3%)	0	0	0
Nervous system disorders	5 (1.7%)	1 (0.3%)	0	1 (0.2%)
Atypical migraine	1 (0.3%)	0	0	0
Cerebellar infarction	1 (0.3%)	0	0	0
Cerebellar stroke	1 (0.3%)	0	0	0
Cerebrovascular accident	1 (0.3%)	0	0	0
Epilepsy	0	1 (0.3%)	0	1 (0.2%)
Haemorrhage intracranial	1 (0.3%)	0	0	0
Headache	1 (0.3%)	0	0	0
Lacunar infarction	1 (0.3%)	0	0	0
Psychiatric disorders	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Anxiety	0	1 (0.3%)	0	1 (0.2%)
Mental status changes	1 (0.3%)	0	0	0
Renal and urinary disorders	2 (0.7%)	0	0	0
Acute kidney injury	1 (0.3%)	0	0	0
Diabetic nephropathy	1 (0.3%)	0	0	0
Reproductive system and breast disorders	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Pelvic organ prolapse	1 (0.3%)	0	0	0
Uterine haemorrhage	0	0	1 (0.3%)	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Chronic obstructive pulmonary disease	0	0	1 (0.3%)	1 (0.2%)
Respiratory failure	0	0	1 (0.3%)	1 (0.2%)
Sleep apnoea syndrome	0	1 (0.3%)	0	1 (0.2%)
Surgical and medical procedures	0	0	2 (0.7%)	2 (0.3%)
Medical induction of coma	0	0	1 (0.3%)	1 (0.2%)
Spinal fusion surgery	0	0	1 (0.3%)	1 (0.2%)
Vascular disorders	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Giant cell arteritis	1 (0.3%)	0	0	0
Hypertension	0	1 (0.3%)	0	1 (0.2%)
Hypertensive emergency	1 (0.3%)	0	0	0

Up to week 64, Non-ocular TEAEs were reported in 368 (62.3%) participants in the All 8mg group (181 [61.8%] in the 8q8/3 group and 187 [62.8%] in the 8q8/5 group) and 189 (62.8%) participants in the 2q4 group (Table 97). The majority of the TEAEs were in the SOC of Infections and infestations;

Nasopharyngitis was the most common TEAE, which was reported in 52 (8.8%) participants in the All 8mg group (25 [8.5%] in the 8q8/3 group and 27 [9.1%] in the 8q8/5 group) and 20 (6.6%) participants in the 2q4 group. All cases of Nasopharyngitis were non-serious, assessed as not related to study intervention, and were mild or moderate intensity. The second most common TEAE was Hypertension under the SOC of Vascular disorders, which was reported in 56 (9.5%) of participants in the All 8mg group (31 [10.6%] and 25 [8.4%] for the 8q8/3 and 8q8/5 groups, respectively) and 15 [5.0%] of participants in the 2q4 group. This is consistent with the imbalance in incidence of medical history of Hypertension with 65.7% in the All 8mg group compared to 62.1% in the 2q4 group. All cases of Hypertension were non-serious, assessed as not related to study intervention, almost all were mild or moderate intensity, and no clinically relevant changes in BP measurements were observed. All other non-ocular TEAEs were reported in <6.0% of participants in any treatment group.

Table 101: Number (%) of participants for non-ocular TEAEs: 10 most frequent PTs in each treatment group with their associated SOCs (safety analysis set)

Primary System Organ Class Preferred term MedDRA version 28.0	**2q4** N=301 (100%)	**8q8/3** N=293 (100%)	**8q8/5** N=298 (100%)	**All 8 mg** N=591 (100%)
Number (%) of participants with ≥ 1 such event	189 (62.8%)	181 (61.8%)	187 (62.8%)	368 (62.3%)
Infections and infestations	92 (30.6%)	83 (28.3%)	93 (31.2%)	176 (29.8%)
Nasopharyngitis	20 (6.6%)	25 (8.5%)	27 (9.1%)	52 (8.8%)
Influenza	13 (4.3%)	11 (3.8%)	6 (2.0%)	17 (2.9%)
Urinary tract infection	13 (4.3%)	8 (2.7%)	15 (5.0%)	23 (3.9%)
COVID-19	9 (3.0%)	17 (5.8%)	12 (4.0%)	29 (4.9%)
Upper respiratory tract infection	8 (2.7%)	8 (2.7%)	3 (1.0%)	11 (1.9%)
Herpes zoster	7 (2.3%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Bronchitis	4 (1.3%)	6 (2.0%)	7 (2.3%)	13 (2.2%)
Pneumonia	4 (1.3%)	6 (2.0%)	5 (1.7%)	11 (1.9%)
Investigations	24 (8.0%)	38 (13.0%)	29 (9.7%)	67 (11.3%)
Blood pressure increased	3 (1.0%)	6 (2.0%)	4 (1.3%)	10 (1.7%)
Metabolism and nutrition disorders	31 (10.3%)	15 (5.1%)	27 (9.1%)	42 (7.1%)
Hyperlipidaemia	9 (3.0%)	3 (1.0%)	3 (1.0%)	6 (1.0%)
Musculoskeletal and connective tissue disorders	32 (10.6%)	35 (11.9%)	25 (8.4%)	60 (10.2%)
Arthralgia	7 (2.3%)	6 (2.0%)	6 (2.0%)	12 (2.0%)
Back pain	7 (2.3%)	3 (1.0%)	5 (1.7%)	8 (1.4%)
Nervous system disorders	25 (8.3%)	28 (9.6%)	26 (8.7%)	54 (9.1%)
Headache	8 (2.7%)	10 (3.4%)	7 (2.3%)	17 (2.9%)
Respiratory, thoracic and mediastinal disorders	18 (6.0%)	21 (7.2%)	11 (3.7%)	32 (5.4%)
Cough	7 (2.3%)	6 (2.0%)	3 (1.0%)	9 (1.5%)
Vascular disorders	22 (7.3%)	39 (13.3%)	31 (10.4%)	70 (11.8%)
Hypertension	15 (5.0%)	31 (10.6%)	25 (8.4%)	56 (9.5%)

No Clinically meaningful differences were observed in type of non-ocular TEAEs or their frequencies between the All 8mg and 2q4 groups.

The results of the subgroup analyses by RVO types (CRVO/HRVO vs. BRVO) for non-ocular TEAEs were similar to those seen in the entire safety population and did not suggest clinically relevant differences among the treatment groups.

For non-ocular TEAEs up to week 36, the most reported SOC were Vascular disorders (5,3% in 2q4 and 8,3% in all 8 mg) and Infections and Infestations (19,3% in 2q4 and 18,8% in all 8 mg) with the PT Hypertension (3,3 % in 2q4, 6,5% in 8q8/3 and 6,7% in 8q8/5) and Nasopharyngitis (3,0 % in 2q4, 5,1% in 8q8/3 and 4,7% in 8q8/5) which were consistent with the study population and observed imbalances in incidence of reported non-ocular medical history between treatment arms (61.9% in the All 8mg group compared to 57.5% in the 2q4 group for Hypertension).

Non-ocular TEAEs were mild (27,9% in 2q4 and 30,6% in All 8 mg) to moderate (16.9% in 2q4 and 15.1% in All 8 mg) in intensity. Severe non-ocular TEAEs were reported mainly in single participants except for Bradycardia and Sepsis (2 participants each in 8q8/3) and type 2 diabetes mellitus (2 participants in the 2q4 group).

Up to week 64, the most reported non-ocular TEAEs were Nasopharyngitis (6.6% in 2q4 arm and 8.8% in all 8 mg) and Hypertension (5.0% in 2q4 arm and 10.6% in all 8 mg group), however all events were non-serious, mostly mild or moderate and not assessed as related to study intervention.

– TEAEs related to study intervention

○ *Ocular study-intervention–related TEAEs in the study eye*

Ocular study intervention-related TEAEs in the study eye were generally reported at a low frequency and mostly were reported in single participants only (table below). The events that were reported for more than 2 participants in any treatment group were IOP increased and Visual acuity reduced. IOP increased was reported in 8 (1.4%) participants in the All 8mg group and 1 (0.3%) participant in the 2q4 group. Visual acuity reduced was reported in 2 (0.7%) participants each in the 8q8/3 group and the 2q4 group. Of the 4 events of Visual acuity reduced judged to be related to study intervention, 2 were resolved, 1 is resolving, and 1 has not resolved by Week 36.

Table 102: TEAEs in the study eye

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	6 (2.0%)	12 (4.1%)	6 (2.0%)	18 (3.0%)
Eye disorders	4 (1.3%)	6 (2.0%)	3 (1.0%)	9 (1.5%)
Anterior chamber disorder	0	1 (0.3%)	0	1 (0.2%)
Blindness	0	0	1 (0.3%)	1 (0.2%)
Conjunctival haemorrhage	0	0	1 (0.3%)	1 (0.2%)
Epiretinal membrane	1 (0.3%)	0	0	0
Eye inflammation	1 (0.3%)	0	0	0
Macular degeneration	2 (0.7%)	0	0	0
Macular oedema	0	1 (0.3%)	0	1 (0.2%)
Macular thickening	0	1 (0.3%)	0	1 (0.2%)
Retinal vasculitis	0	0	1 (0.3%)	1 (0.2%)
Visual acuity reduced	2 (0.7%)	2 (0.7%)	0	2 (0.3%)
Vitreous detachment	0	1 (0.3%)	0	1 (0.2%)
Infections and infestations	1 (0.3%)	0	0	0
Endophthalmitis	1 (0.3%)	0	0	0
Injury, poisoning and procedural complications	0	1 (0.3%)	0	1 (0.2%)
Intra-ocular injection complication	0	1 (0.3%)	0	1 (0.2%)
Investigations	1 (0.3%)	5 (1.7%)	3 (1.0%)	8 (1.4%)
Intraocular pressure increased	1 (0.3%)	5 (1.7%)	3 (1.0%)	8 (1.4%)

Up to week 64, ocular TEAEs in the study eye assessed as related to study intervention were slightly more reported in all 8 mg arm (3.7% vs 2.0% in 2q4 arm).

Ocular TEAEs related to study-intervention were mainly reported in single participants except for Visual acuity reduced (mild, non-serious, recovered and dose not changed in both patients in 8q8/3 group and moderate, serious, not recovered/resolved and dose interrupted and moderate, not serious, recovering/resolving and dose not changed in 2q4 arm), Macular degeneration (2 participants in 2q4 arm, the events were mild or moderate, not serious, not recovered/not resolved and drug interrupted) and IOP increased (in 9 participants in total, 0.3% in 2q4 and 1.4% in All 8 mg).

○ *Non-ocular study-intervention-related TEAEs*

Non-ocular study intervention-related TEAEs was reported in 2 (0.7%) participants in the 8q8/3 group (Atrioventricular block first degree and Headache, respectively), and 1 (0.3%) participant each in the 8q8/5 group (Rash) and 2q4 group (Haemoglobin increased).

Up to week 64, non-ocular study intervention related TEAEs were reported in 2 participants in 2q4 arm, 3 participants in 8q8/3 and 2 participants in 8q8/5 groups.

Non-ocular TEAEs related to study intervention were reported in two participants in 8q8/3 Atrioventricular block first degree (mild, dose not changed, PR interval increased not significant with new ECG normal) and Headache (also assessed as related to protocol required procedure, moderate, dose not changed and recovered/resolved), 1 participant in 2q4 Haemoglobin increased (severe, drug interrupted, non-serious, recovered/resolved) and 1 participant in 8q8/5 Rash (mild, drug interrupted, non-serious, recovered/resolved).

Between week 36 and week 64, 3 additional non-ocular TEAEs were assessed as related to study intervention (one in each treatment arms).

– TEAEs related to the IVT injection procedure

○ *Ocular IVT-injection related TEAEs in the study eye*

The incidence of ocular TEAEs related to IVT injection procedure in the study eye were generally low, but slightly higher in the All 8mg group (10.7%) than in the 2q4 group (6.3%) (Table 98). Most of the events were reported for single participants only. The most common ocular IVT-injection-related TEAEs, reported in ≥5 participants in total, were Conjunctival haemorrhage, IOP increased, and Eye pain. All events were non-serious except for 6 events, which were serious (Endophthalmitis in 2 participants in the 2q4 group and 1 participant in the 8q8/3 group, Macular hole and Retinal detachment each in 1 participant in the 2q4 group, and Cataract in 1 participant in the 8q8/5 group).

Table 103: Ocular treatment-emergent intravitreal injection procedure-related adverse events of study eye (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	19 (6.3%)	38 (13.0%)	25 (8.4%)	63 (10.7%)
Eye disorders	13 (4.3%)	25 (8.5%)	17 (5.7%)	42 (7.1%)
Blepharitis	0	1 (0.3%)	0	1 (0.2%)
Blindness	0	0	1 (0.3%)	1 (0.2%)
Cataract	0	0	1 (0.3%)	1 (0.2%)
Conjunctival haemorrhage	5 (1.7%)	8 (2.7%)	6 (2.0%)	14 (2.4%)
Conjunctival hyperaemia	0	0	1 (0.3%)	1 (0.2%)
Conjunctival irritation	1 (0.3%)	0	0	0
Conjunctival oedema	1 (0.3%)	0	0	0
Conjunctival suffusion	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Corneal disorder	0	1 (0.3%)	0	1 (0.2%)
Dry eye	0	1 (0.3%)	0	1 (0.2%)
Epiretinal membrane	0	0	2 (0.7%)	2 (0.3%)
Eye pain	2 (0.7%)	3 (1.0%)	2 (0.7%)	5 (0.8%)
Lenticular opacities	0	0	1 (0.3%)	1 (0.2%)
Macular hole	1 (0.3%)	0	0	0
Macular oedema	0	1 (0.3%)	0	1 (0.2%)
Ocular hypertension	0	2 (0.7%)	1 (0.3%)	3 (0.5%)
Punctate keratitis	2 (0.7%)	2 (0.7%)	0	2 (0.3%)
Retinal artery occlusion	0	1 (0.3%)	0	1 (0.2%)
Retinal detachment	1 (0.3%)	0	0	0
Retinal tear	0	1 (0.3%)	0	1 (0.2%)
Vitreoretinal traction syndrome	0	1 (0.3%)	0	1 (0.2%)
Vitreous detachment	0	3 (1.0%)	1 (0.3%)	4 (0.7%)
Vitreous floaters	2 (0.7%)	2 (0.7%)	0	2 (0.3%)
Vitreous haemorrhage	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Vitreous opacities	0	0	1 (0.3%)	1 (0.2%)
General disorders and administration site conditions	1 (0.3%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Injection site irritation	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Injection site pain	0	0	1 (0.3%)	1 (0.2%)
Pain	0	2 (0.7%)	0	2 (0.3%)
Sensation of foreign body	0	1 (0.3%)	0	1 (0.2%)
Infections and infestations	2 (0.7%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Conjunctivitis	0	0	1 (0.3%)	1 (0.2%)
Endophthalmitis	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	1 (0.3%)	3 (1.0%)	0	3 (0.5%)
Injury corneal	0	1 (0.3%)	0	1 (0.2%)
Intra-ocular injection complication	1 (0.3%)	2 (0.7%)	0	2 (0.3%)
Investigations	3 (1.0%)	9 (3.1%)	6 (2.0%)	15 (2.5%)
Intraocular pressure increased	3 (1.0%)	9 (3.1%)	6 (2.0%)	15 (2.5%)

- ***Non-ocular IVT-injection-related TEAEs***

Non-ocular IVT-injection-related TEAEs through Week 36 were reported in 1 (0.3%) participant in the 2q4 group (Headache).

Injection-related ocular TEAEs were slightly more reported in all 8mg group (10.7% vs 6.3% in 2q4). The most reported PT (≥5 participants in total) were Conjunctival haemorrhage (1.7% in 2q4 and 2.4% in All 8 mg), IOP increased (1.0% in 2q4 and 2.5% in All 8 mg) and Eye pain (0.7% in 2q4 and 0.8% in All 8 mg).

Non-ocular TEAEs were reported in one participant in 2q4 who presented multiple events of non-serious mild headache (all recovered, and dose not changed).

- **TEAEs related to protocol-required procedures**

    - ***Ocular TEAEs related to protocol-required procedures in the study eye***

Ocular protocol-required procedures-related TEAEs in the study eye were reported in 11 (1.9%) participants in the All 8mg group (5 [1.7%] and 6 [2.0%] for the 8q8/3 and 8q8/5 groups, respectively) and 3 (1.0%) participants in the 2q4 group. All the events were reported for single participants only except for IOP increased (2 participants in the 8q8/3 and 8q8/5 groups, respectively) and Conjunctival haemorrhage (1 participant in each of the treatment group).

Ocular protocol-required procedures related TEAEs in the study eye were slightly more reported in comparable proportion between all 8 mg group (2.0%) and 2q4 group (1.9%). All events occurred in single participants except IOP increased (4 participants in all 8 mg group) and Conjunctival haemorrhage (one participants in each group).

    - ***Non-ocular TEAEs related to protocol required procedures***

Non-ocular protocol-required procedures-related TEAEs through Week 36 were reported in 9 (1.5%) participants in All 8mg group (4 [1.4%] and 5 [1.7%] for the 8q8/3 and 8q8/5 groups, respectively) and 3 (1.0%) participants in the 2q4 group (QUASAR W36 CSR). All the events were reported in single participants only except for Nausea (3 participants in the 8q8/5 group, and 1 participant each in the 8q8/3 group and 2q/4 group).

Non-ocular TEAE related to protocol required procedure were reported in comparable proportions (1,0% in 2q4 and 1,5% in all 8 mg group) and occurred in single participants except for Nausea.

- **TEAEs related to 2 mg aflibercept in the fellow eye**

Once the fellow eye received 2 mg aflibercept treatment during the study, TEAEs and serious TEAEs were also assessed as related/not related to the commercial 2 mg aflibercept in the fellow eye.

No ocular or non-ocular TEAE related to fellow eye treatment with 2 mg aflibercept was reported in any treatment group through Week 36.

Serious adverse event/deaths/other significant events

Deaths

Through Week 36, there were 7 deaths reported in this study, evenly distributed across the treatment groups (Table 99), and all were associated with an SAE. None of the underlying SAEs were assessed to be related to study intervention or study procedure. All AEs with fatal outcome were reported for single participants and all were TEAEs except for the Bronchitis with fatal outcome for the participant in the 8q8/5 group which was a post-treatment AE.

Overall, the deaths reported were consistent with concurrent medical conditions and the complications of these conditions associated with an older population.

Table 104: Deaths: number of participants with adverse events with fatal outcome (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Infections and infestations	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Bronchitis	0	0	1 (0.3%)	1 (0.2%)
Pneumonia	1 (0.3%)	0	0	0
Sepsis	0	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	0	0	1 (0.3%)	1 (0.2%)
Brain herniation	0	0	1 (0.3%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Oesophageal carcinoma	0	1 (0.3%)	0	1 (0.2%)
Prostate cancer metastatic	0	0	1 (0.3%)	1 (0.2%)
Nervous system disorders	1 (0.3%)	0	0	0
Haemorrhage intracranial	1 (0.3%)	0	0	0

Up to week 64, there were 10 deaths reported in this study, and all were associated with an SAE. One event of Myocardial ischaemia in an elderly participant in the 8q8/5 group who had a medical history of dyslipidemia and hypertension was assessed as related to the study intervention. All other events were assessed as not related to study intervention, IVT injection procedure or protocol-required procedure. All AEs with fatal outcomes were reported for single participants and all were TEAEs except for the events of Bronchitis and Cardiogenic shock, which were post-treatment AEs each in one participant in the 8q8/5 group. Overall, the deaths reported were consistent with concurrent medical conditions and the complications of these conditions associated with an older population.

Table 105: Deaths: number of participants with adverse events with fatal outcome by primary system organ class and preferred term (safety analysis set)

Primary system organ class Preferred term MedDRA version 28.0	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8 mg N=591 (100%)
Number (%) of participants with ≥ 1 one such event	3 (1.0%)	2 (0.7%)	5 (1.7%)	7 (1.2%)
Cardiac disorders	0	0	2 (0.7%)	2 (0.3%)
Cardiogenic shock	0	0	1 (0.3%)	1 (0.2%)
Myocardial ischaemia	0	0	1 (0.3%)	1 (0.2%)
Infections and infestations	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Bronchitis	0	0	1 (0.3%)	1 (0.2%)
Pneumonia	1 (0.3%)	0	0	0
Sepsis	0	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	0	0	1 (0.3%)	1 (0.2%)
Brain herniation	0	0	1 (0.3%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Oesophageal carcinoma	0	1 (0.3%)	0	1 (0.2%)
Prostate cancer metastatic	0	0	1 (0.3%)	1 (0.2%)
Nervous system disorders	1 (0.3%)	0	0	0
Haemorrhage intracranial	1 (0.3%)	0	0	0
Psychiatric disorders	1 (0.3%)	0	0	0
Completed suicide	1 (0.3%)	0	0	0

Through week 36, 7 deaths occurred in comparable proportions between treatment arms (0.7% in 2q4 and 8q8/3 and 1.0% in 8q8/5 group). None of the deaths were assessed as related to study intervention or study procedure.

Between week 36 and 64, three additional deaths occurred. None were assessed as related to study intervention.

– Other serious adverse events

○ *Ocular serious TEAEs in the study eye*

The incidence of ocular serious TEAEs in the study eye was low in all treatment groups and numerically lower in the All 8mg group (1.2%) than in the 2q4 group (2.3%). Most of these events were reported in single participants except for Endophthalmitis (2 participants in the 2q/4 group and 1 in the 8q8/3 group), Macular hole (2 participants in the 2q4 group), and Visual acuity reduced (1 participant each in the 8q8/5 group and the 2q/4 group) (Table 101). The maximum intensity of these SAEs was mostly moderate or severe.

Three of the events were assessed to be related to the study intervention by the investigator: Retinal vasculitis in 1 participant in the 8q8/5 group, and Visual acuity reduced and Endophthalmitis each in 1 participant in the 2q4 group. Six of the events were assessed to be related to IVT injection procedure by the investigator: Endophthalmitis in 2 participants in the 2q4 group and 1 participant in the 8q8/3 group, Macular hole and Retinal detachment each in 1 participant in the 2q4 group, and Cataract in 1 participant in the 8q8/5 group.

The outcomes for all events of Endophthalmitis and the event of Cataract were recovered/resolved or recovered/resolved with sequela. The outcome for the event of Retinal detachment was recovering/resolving. The outcomes for the events of Macular hole and Visual acuity reduced were not recovered/not resolved at the time of the week 36 data cut.

The event of Retinal vasculitis (not reported as an occlusive event) was experienced by a participant in the 8q8/5 group approximately 1 month after the second dose of study intervention. There were no signs or symptoms of a concurrent intraocular infection, and no medical history of systemic vasculitis was reported. A systemic cause (e.g., Behcet disease or others) was not found based on performed laboratory investigations (ESR/CRP/PPD/ACE/test for VDRL/Toxoplasmosis/HIV/HSV/RF/ANA/ANCA). Study intervention was withdrawn, and the participant remained in the study for follow-up; the participant was started on dexamethasone intravitreal implant (Ozurdex) treatment and received intravitreal anti-VEGF treatment (ranibizumab, bevacizumab) and improved. The review of the examination with FA/fundoscopy and OCT showed vessel staining and multiple cotton wool spots without inflammatory cells. Some evidence of vessel staining was already noted at baseline, which is typical for RVO. At the time of event, larger veins showed more prominent staining, but no evidence of significant increase in non-perfusion. There were no indications of worsening of RVO, and no other explanation for why vision was reduced. Further follow-up information will be collected.

Table 106: Ocular serious TEAEs in the study eye (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	7 (2.3%)	3 (1.0%)	4 (1.3%)	7 (1.2%)
Eye disorders	5 (1.7%)	0	4 (1.3%)	4 (0.7%)
Cataract	0	0	1 (0.3%)	1 (0.2%)
Macular hole	2 (0.7%)	0	0	0
Retinal artery occlusion	1 (0.3%)	0	0	0
Retinal detachment	1 (0.3%)	0	0	0
Retinal vasculitis	0	0	1 (0.3%)	1 (0.2%)
Retinal vein occlusion	0	0	1 (0.3%)	1 (0.2%)
Visual acuity reduced	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
General disorders and administration site conditions	0	1 (0.3%)	0	1 (0.2%)
Oedema	0	1 (0.3%)	0	1 (0.2%)
Infections and infestations	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Endophthalmitis	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	0	1 (0.3%)	0	1 (0.2%)
Skin laceration	0	1 (0.3%)	0	1 (0.2%)

Up to week 64, the proportion of participants with ocular serious TEAEs in the study eye was low in all treatment groups and numerically lower in the All 8mg group (10 [1.7%]: 5 [1.7%] for the 8q8/3 and 8q8/5 groups, respectively) than in the 2q4 group 8 (2.7%) participants. Most of these events were reported in single participants except for Endophthalmitis (3 participants in the 2q/4 group and 1 in the 8q8/3 group), Macular hole (2 participants in the 2q4 group), and Visual acuity reduced (1 participant each in the 8q8/5 group and the 2q/4 group). The maximum intensity of these SAEs was mostly moderate (5 [0.8%] participants in the All 8mg group and 4 [1.3%] participants in the 2q4 group) or severe (4 [0.7%] in the All 8mg group and 4 [1.3%] participants in the 2q4 group).

Seven of the events were assessed to be related to IVT injection procedure (Endophthalmitis in 3 participants in the 2q4 group and 1 participant in the 8q8/3 group, Macular hole and Retinal detachment each in 1 participant in the 2q4 group, and Cataract in 1 participant in the 8q8/5 group). Three of the events were assessed to be related to the study intervention (Retinal vasculitis in 1 participant in the 8q8/5 group, and Visual acuity reduced and Endophthalmitis each in 1 participant in the 2q4 group).

Table 107: Ocular serious TEAEs in the study eye: number of participants by primary system organ class and preferred term (safety analysis set)

Primary system organ class Preferred term MedDRA version 28.0	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	8 (2.7%)	5 (1.7%)	5 (1.7%)	10 (1.7%)
Eye disorders	5 (1.7%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Cataract	0	0	1 (0.3%)	1 (0.2%)
Glaucoma	0	1 (0.3%)	0	1 (0.2%)
Macular hole	2 (0.7%)	0	0	0
Retinal artery occlusion	1 (0.3%)	0	0	0
Retinal detachment	1 (0.3%)	0	0	0
Retinal vasculitis	0	0	1 (0.3%)	1 (0.2%)
Retinal vein occlusion	0	0	1 (0.3%)	1 (0.2%)
Visual acuity reduced	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Vitritis	0	1 (0.3%)	0	1 (0.2%)
General disorders and administration site conditions	0	1 (0.3%)	0	1 (0.2%)
Oedema	0	1 (0.3%)	0	1 (0.2%)
Infections and infestations	3 (1.0%)	1 (0.3%)	0	1 (0.2%)
Endophthalmitis	3 (1.0%)	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Posterior capsule rupture	0	0	1 (0.3%)	1 (0.2%)
Skin laceration	0	1 (0.3%)	0	1 (0.2%)

The results of the subgroup analyses by RVO types for ocular serious TEAEs in the study eye show slightly higher incidences in the CRVO/HRVO subgroup than in the BRVO subgroup, which was mainly driven by

more PTs types were reported in the CRVO/HRVO subgroup, for which almost all were reported in single participants.

Ocular SAE in the study eye occurred in slightly higher proportions in 2q4 group (2.3% vs 1.2% in all 8 mg group). All events were reported in single participants across treatment groups except Endophthalmitis (2 participants in 2q4 and 1 in 8q8/3 groups), Visual acuity reduced (1 participant in 8q8/5 and 2q4 groups) and Macular hole (2 participants in 2q4).

Ocular SAEs in the study eye were mostly moderate (1.3% in 2q4 and 0.7% in All 8 mg) to severe (1.0% in 2q4 and 0.3% in All 8 m). Six events were assessed as related to IVT injection procedure (Endophthalmitis in 2 participants in the 2q4 group and 1 participant in the 8q8/3 group, Macular hole and Retinal detachment each in 1 participant in the 2q4 group, and Cataract in 1 participant in the 8q8/5 group) and three events to study intervention (Retinal vasculitis in 1 participant in the 8q8/5 group, and Visual acuity reduced and Endophthalmitis each in 1 participant in the 2q4 group). The outcomes for all events of Endophthalmitis and the event of Cataract were recovered/resolved or recovered/resolved with sequela. The outcome for the event of Retinal detachment was recovering/resolving. The outcomes for the events of Macular hole and Visual acuity reduced were not recovered/not resolved at the time of the week 36 data cut.

Up to week 64, ocular TESAE in the study eye occurred in low proportions, 2.7% participants in 2q4 arm and 1.7% in all 8 mg group. Serious ocular TEAEs were assessed as related to IVT injection for seven events (Endophthalmitis in 3 participants in the 2q4 group and 1 participant in the 8q8/3 group, Macular hole and Retinal detachment each in 1 participant in the 2q4 group, and Cataract in 1 participant in the 8q8/5 group) and assessed as related to study intervention in three events (Retinal vasculitis in 1 participant in the 8q8/5 group, and Visual acuity reduced and Endophthalmitis each in 1 participant in the 2q4 group). The maximum intensity was moderate (5 [0.8%] participants in the All 8mg group and 4 [1.3%] participants in the 2q4 group) or severe (4 [0.7%] in the All 8mg group and 4 [1.3%] participants in the 2q4 group). Seven events were assessed as related to IVT injection and three assessed as related to study intervention. Events were recovered/resolved for 4 events, recovered with sequelae for 3 events and not recovered/not resolved for two events.

- ***Ocular serious TEAEs in the fellow eye***

Ocular serious TEAEs in the fellow eye were reported in 1 (0.3%) participant in the 8q8/3 group with a total of 3 events (Choroidal detachment, Flat anterior chamber of eye, and Glaucoma). All three events were severe in intensity, but none were assessed to be related to study intervention or IVT injection procedure. The events of Flat anterior chamber of eye and Glaucoma were resolved, and the Choroidal detachment is resolving by Week 36.

- ***Non-ocular serious TEAEs***

The incidences of non-ocular serious TEAEs were similar across the treatment groups. The majority of the events were reported in no more than one participant. Table 103 presents the events that were reported in >1 participant in any treatment group. Across the treatment groups, the most frequent non-ocular serious TEAEs was Pneumonia, which was reported in 1 (0.3%) participant in the 8q8/3 group and 2 (0.7%) participants in the 2q4 group. None of the non-ocular serious TEAEs was assessed to be related to study intervention or IVT injection procedure. The maximum intensity of these SAEs was mostly moderate or severe.

Table 108: Non-ocular treatment-emergent SAEs occurring in ≥2 participant in all treatment group (safety analysis set)

Primary System Organ Class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	25 (8.3%)	21 (7.2%)	22 (7.4%)	43 (7.3%)
Cardiac disorders				
Bradycardia	0	2 (0.7%)	0	2 (0.3%)
Infections and infestations				
COVID-19	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Diverticulitis	0	2 (0.7%)	0	2 (0.3%)
Herpes zoster	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Osteomyelitis	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Pneumonia	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Sepsis	0	2 (0.7%)	0	2 (0.3%)
Metabolism and nutrition disorders				
Type 2 diabetes mellitus	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Nervous system disorders				
Epilepsy	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Renal and urinary disorders				
Diabetic nephropathy	1 (0.3%)	0	1 (0.3%)	1 (0.2%)

Up to week 64, non-ocular serious TEAEs were reported with similar frequencies across the treatment groups: 66 (11.2%) participants in the All 8mg group (33 [11.3%] and 33 [11.1%] for the 8q8/3 and 8q8/5 groups, respectively) and 36 (12.0%) participants in the 2q4 group. The majority of these TEAEs were reported in single participants only. Across the treatment groups, the most frequent non-ocular serious TEAE was Pneumonia, which was reported in 2 (0.7%) participants each in the 8q8/3 group and the 2q4 group, and 1 (0.3%) participant in the 8q8/5 group. None of the non-ocular serious TEAEs was assessed to be related IVT injection procedure and two of the events was assessed to be related to study intervention (Myocardial infarction for 1 participant in the 8q8/3 group who had a medical history of 2 prior myocardial infarctions and also underlying diabetes mellitus, and Myocardial ischemia with fatal outcome for 1 participant in the 8q8/5 group [see Section 4.3.1]). Study intervention was interrupted by the Myocardial infarction, and the recorded outcome was not recovered/not resolved at the time of this report. The maximum intensity of these SAEs was mostly moderate (28 [4.7%] participants in the All 8mg group and 14 [4.7%] in 2q4 group) or severe (30 [5.1%] participants in the All 8mg group and 19 [6.3%] in 2q4 group).

Table 109: Non-ocular treatment-emergent SAEs occurring in >1 participant in all treatment group with their associated SOCs through week 64 (safety analysis set)

Primary System Organ Class Preferred term MedDRA version 28.0	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	36 (12.0%)	33 (11.3%)	33 (11.1%)	66 (11.2%)
Cardiac disorders	2 (0.7%)	6 (2.0%)	6 (2.0%)	12 (2.0%)
Atrial fibrillation	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Bradycardia	0	2 (0.7%)	0	2 (0.3%)
Coronary artery disease	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Myocardial infarction	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Infections and infestations	6 (2.0%)	8 (2.7%)	12 (4.0%)	20 (3.4%)
COVID-19	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Diverticulitis	0	2 (0.7%)	1 (0.3%)	3 (0.5%)
Herpes zoster	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Osteomyelitis	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Pneumonia	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Sepsis	0	2 (0.7%)	1 (0.3%)	3 (0.5%)
Injury, poisoning and procedural complications	5 (1.7%)	4 (1.4%)	3 (1.0%)	7 (1.2%)
Multiple injuries	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Rib fracture	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Metabolism and nutrition disorders	2 (0.7%)	0	1 (0.3%)	1 (0.2%)
Type 2 diabetes mellitus	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Osteoarthritis	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Nervous system disorders	7 (2.3%)	4 (1.4%)	3 (1.0%)	7 (1.2%)
Epilepsy	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Seizure	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Renal and urinary disorders	2 (0.7%)	1 (0.3%)	3 (1.0%)	4 (0.7%)
Diabetic nephropathy	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Ureterolithiasis	0	1 (0.3%)	1 (0.3%)	2 (0.3%)

The results of the subgroup analyses by RVO types for non-ocular serious TEAEs show slightly higher incidences in the CRVO/HRVO subgroup than in the BRVO subgroup. This was mainly driven by more PTs under the SOC Infections and infestations were reported in the CRVO/HRVO subgroup, and most of these events were reported in single participants.

Non-ocular SAEs were reported in comparable proportions between treatment groups (7.3% in all 8 mg group and 8.3% in 2q4 group). Non-ocular SAEs were mainly severe (3.6% in All 8 mg and 4.7% in 2q4 group) to moderate (2.9% in All 8 mg and 3.3% in 2q4 group). The most frequent non-ocular serious TEAEs was Pneumonia, which was reported in 1 (0.3%) participant in the 8q8/3 group and 2 (0.7%) participants in the 2q4 group.

Up to week 64, non-ocular TESAEs were reported in similar proportions, 12.0% in 2q4 arm and 11.2% in all 8 mg arm.

None of the non-ocular serious TEAEs was assessed to be related to IVT injection procedure and two were assessed as related to study intervention (Myocardial infarction for 1 participant in the 8q8/3 group who had a medical history of 2 prior myocardial infarctions and also underlying diabetes mellitus, and Myocardial ischemia with fatal outcome for 1 participant in the 8q8/5 group).

– Analysis of adverse events by organ system or syndrome

○ *Adverse events of special interest*

The incidence of AESI was low and numerically lower in the All 8mg group (1.0%) than in the 2q4 group (3.0%). All AESI were reported in no more than one participant except for Coronary artery disease (1 participant each in the 8q8/3 and 2q4 groups) and Cerebral infarction (1 participant each in the 8q8/5 and 2q4 groups) (Table 105).

Table 110: Treatment-emergent adverse events of special interest (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	9 (3.0%)	1 (0.3%)	5 (1.7%)	6 (1.0%)
Cardiac disorders	2 (0.7%)	1 (0.3%)	2 (0.7%)	3 (0.5%)
Acute coronary syndrome	0	0	1 (0.3%)	1 (0.2%)
Acute myocardial infarction	1 (0.3%)	0	0	0
Coronary artery disease	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Myocardial infarction	0	0	1 (0.3%)	1 (0.2%)
Eye disorders	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Retinal artery embolism	0	0	1 (0.3%)	1 (0.2%)
Retinal artery occlusion	1 (0.3%)	0	0	0
Nervous system disorders	6 (2.0%)	0	1 (0.3%)	1 (0.2%)
Atypical migraine	1 (0.3%)	0	0	0
Carotid artery occlusion	1 (0.3%)	0	0	0
Cerebellar infarction	1 (0.3%)	0	0	0
Cerebellar stroke	1 (0.3%)	0	0	0
Cerebral infarction	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Cerebrovascular accident	1 (0.3%)	0	0	0
Haemorrhage intracranial	1 (0.3%)	0	0	0
Lacunar infarction	1 (0.3%)	0	0	0
Vascular disorders	0	0	1 (0.3%)	1 (0.2%)
Peripheral artery occlusion	0	0	1 (0.3%)	1 (0.2%)

Table displays adverse events of special interest as collected on the CRF. Adverse Event of Special Interest (AESI) are arterial
thromboembolic events including cerebrovascular ischemic events and cardiovascular ischemic events.

Up to week 64, nine (1.5%) participants in the All 8mg group (2 [0.7%] and 7 [2.3%] for the 8q8/3 and 8q8/5 groups, respectively) and 6 (2.0%) participants in the 2q4 group reported adjudicated APTC events.

Table 111: Treatment-emergent adverse events: number of participants with APTC event by primary system organ class and preferred term (safety analysis set)

Primary system organ class Preferred term MedDRA version 28.0	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	6 (2.0%)	2 (0.7%)	7 (2.3%)	9 (1.5%)
Cardiac disorders	2 (0.7%)	1 (0.3%)	4 (1.3%)	5 (0.8%)
Acute coronary syndrome	0	0	1 (0.3%)	1 (0.2%)
Acute myocardial infarction	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Myocardial infarction	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Myocardial ischaemia	0	0	1 (0.3%)	1 (0.2%)
Eye disorders	0	1 (0.3%)	0	1 (0.2%)
Amaurosis fugax	0	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	0	0	1 (0.3%)	1 (0.2%)
Brain herniation	0	0	1 (0.3%)	1 (0.2%)
Nervous system disorders	4 (1.3%)	0	2 (0.7%)	2 (0.3%)
Cerebellar infarction	1 (0.3%)	0	0	0
Cerebellar stroke	1 (0.3%)	0	0	0
Cerebral infarction	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Cerebrovascular accident	1 (0.3%)	0	0	0
Haemorrhagic stroke	0	0	1 (0.3%)	1 (0.2%)

The proportion of participants with these events was low and numerically lower in the 8q8/3 group (2 [0.7%] participants) than in the 8q8/5 group (8 [2.7%]) and the 2q4 group (9 [3.0%]). All events were reported in single participants except for Coronary artery disease (1 participant in each of the 2q4, 8q8/3 and 8q8/5 groups), Myocardial infarction (1 participant in each of the 8q8/3 and 8q8/5 groups) and

Acute myocardial infarction and Cerebral infarction (each in 1 participant in the 8q8/5 and 2q4 groups, respectively).

Table 112: Treatment-emergent adverse events of special interest (ATEs): number of participants by primary system organ class and preferred term (safety analysis set)

Primary system organ class **Preferred term** MedDRA version 28.0	**2q4** N=301 (100%)	**8q8/3** N=293 (100%)	**8q8/5** N=298 (100%)	**All 8mg** N=591 (100%)
Number (%) of participants with ≥ 1 such event	9 (3.0%)	2 (0.7%)	8 (2.7%)	10 (1.7%)
Cardiac disorders	2 (0.7%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Acute coronary syndrome	0	0	1 (0.3%)	1 (0.2%)
Acute myocardial infarction	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Coronary artery disease	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Myocardial infarction	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Myocardial ischaemia	0	0	1 (0.3%)	1 (0.2%)
Eye disorders	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Retinal artery embolism	0	0	1 (0.3%)	1 (0.2%)
Retinal artery occlusion	1 (0.3%)	0	0	0
Nervous system disorders	6 (2.0%)	0	2 (0.7%)	2 (0.3%)
Atypical migraine	1 (0.3%)	0	0	0
Carotid artery occlusion	1 (0.3%)	0	0	0
Cerebellar infarction	1 (0.3%)	0	0	0
Cerebellar stroke	1 (0.3%)	0	0	0
Cerebral infarction	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Cerebrovascular accident	1 (0.3%)	0	0	0
Haemorrhage intracranial	1 (0.3%)	0	0	0
Haemorrhagic stroke	0	0	1 (0.3%)	1 (0.2%)
Lacunar infarction	1 (0.3%)	0	0	0
Transient ischaemic attack	1 (0.3%)	0	0	0
Vascular disorders	0	0	1 (0.3%)	1 (0.2%)
Peripheral artery occlusion	0	0	1 (0.3%)	1 (0.2%)

Table displays adverse events of special interest as collected on the CRF. Adverse Event of Special Interest (AESI) are arterial thromboembolic events including cerebrovascular ischemic events and cardiovascular ischemic events.

AESI were reported in higher proportions in 2q4 group (3.0% vs 1.0% in all 8 mg group) and were reported in single participants except for Coronary artery disease (1 participant each in the 8q8/3 and 2q4 groups) and Cerebral infarction (1 participant each in the 8q8/5 and 2q4 groups).

Up to week 64, APTC events occurred in 8q8/3 group (2 [0.7%] participants),8q8/5 group (8 [2.7%]) and 2q4 group (9 [3.0%]) and in single participants except Coronary artery disease (1 participant in each of the 2q4, 8q8/3 and 8q8/5 groups), Myocardial infarction (1 participant in each of the 8q8/3 and 8q8/5 groups) and Acute myocardial infarction and Cerebral infarction (each in 1 participant in the 8q8/5 and 2q4 groups, respectively).

- ***TEAEs related to Intraocular inflammation in the study eye***

The proportion of participants with TEAEs related to Intraocular inflammation in the study eye was low and generally similar among the treatment groups (4 [1.3%] participants in the 2q4 group, 2 [0.7%] in the 8q8/3 group, and 1 [0.3%] in the 8q8/5 group) (Table 108). Most of these events were mild or moderate in intensity and all were considered recovered or considered recovered with sequela. There were 3 participants with serious TEAEs related to Intraocular inflammation, 2 (0.7%) in the 2q4 group and 1 (0.3%) in the 8q8/3 group. All serious TEAEs were events of Endophthalmitis and all were assessed by the investigator to be related to the IVT injection procedure, with 1 event in the 2q4 group also assessed as related to study intervention.

Table 113: Treatment-emergent adverse events: Intraocular inflammation of study eye (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	4 (1.3%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Eye disorders	2 (0.7%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Anterior chamber cell	1 (0.3%)	0	0	0
Eye inflammation	1 (0.3%)	0	0	0
Iritis	0	1 (0.3%)	0	1 (0.2%)
Uveitis	0	0	1 (0.3%)	1 (0.2%)
Infections and infestations	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Endophthalmitis	2 (0.7%)	1 (0.3%)	0	1 (0.2%)

Up to week 64, similar tendencies could be observed.

Table 114: Treatment-emergent adverse events: number of participants with Intraocular inflammation of study eye by primary system organ class and preferred term (safety analysis set)

Primary system organ class Preferred term MedDRA version 28.0	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with ≥ 1 such event	5 (1.7%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Eye disorders	2 (0.7%)	3 (1.0%)	2 (0.7%)	5 (0.8%)
Anterior chamber cell	1 (0.3%)	0	0	0
Eye inflammation	1 (0.3%)	0	0	0
Iritis	0	1 (0.3%)	0	1 (0.2%)
Uveitis	0	0	2 (0.7%)	2 (0.3%)
Vitritis	0	2 (0.7%)	0	2 (0.3%)
Infections and infestations	3 (1.0%)	1 (0.3%)	0	1 (0.2%)
Endophthalmitis	3 (1.0%)	1 (0.3%)	0	1 (0.2%)

Ocular TEAEs related to intraocular inflammation were low across treatment group and seen in higher proportion in 2q4 group (1.3% vs 0.5% in all 8 mg group). All events were reported in single participants except Endophthalmitis and were mainly moderate or mild and recovered/resolved. In 2q4 group, both cases of Endophthalmitis were moderate, serious, related to injection procedure (one was also related to study intervention), recovered/resolved with sequelae for one and dose interrupted for one. In 8q8/3 group, the case of Endophthalmitis was severe, serious, related to injection procedure and recovered/resolved with sequelae with dose not changed. The case of Eye inflammation in 2q4 was moderate, non-serious, related to study intervention, recovered/resolved with dose not changed. The case of Anterior chamber cell in 2q4 was non-serious, mild, recovered/resolved and not related. The event of Uveitis in 8q8/5 group occurred twice in one participant, both events were non-serious, moderate, recovered/resolved and assessed as not related. The event of Iritis in 8q8/3 was non-serious, mild, recovered/resolved and assessed as not related. Similar tendencies were observed up to week 64 (1.7% in 2q4 arm vs 1.0 % in all 8 mg group).

- ***TEAEs related to Cataract in the study eye***

The proportion of participants with TEAEs related to Cataract was similar between the treatment groups (10 [3.3%] participants in the 2q4 group and 20 [3.4%] participants in the All 8 mg group) (Table 110). Most of these events were mild or moderate in intensity. 1 serious TEAE related to Cataract in the study eye was reported in the 8q8/5 group. This serious TEAE was assessed by the investigator as related to the IVT injection procedure, and it resolved with sequelae. Of note, Cataract was a frequent medical history finding, reported in 48.9% of participants in the All 8mg group and 49.2% of participants in the 2q4 group.

Table 115: Treatment-emergent adverse events: cataract in study eye (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	10 (3.3%)	8 (2.7%)	12 (4.0%)	20 (3.4%)
Eye disorders	10 (3.3%)	8 (2.7%)	12 (4.0%)	20 (3.4%)
Cataract	9 (3.0%)	5 (1.7%)	10 (3.4%)	15 (2.5%)
Cataract cortical	0	2 (0.7%)	0	2 (0.3%)
Cataract nuclear	0	0	1 (0.3%)	1 (0.2%)
Lenticular opacities	0	0	2 (0.7%)	2 (0.3%)
Posterior capsule opacification	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)

Cataract was a frequent medical history reported in comparable proportions (48.9% of participants in the All 8mg group and 49.2% of participants in the 2q4 group). Events of Cataract were reported in similar proportions between all 8 mg group (3.3% in 2q4 group and 3.4% in all 8 mg). Events of Cataract were mainly mild (1.3% in 2q4 group and 2.9% in all 8 mg group) and not recovered/ not resolved (1.3% in 2q4 group and 3.0% in all 8 mg group) through Week 36.

- ***TEAEs related to IOP increased in the study eye***

TEAEs related to IOP increased in the study eye were reported in 9 (3.0%) participants in the 2q4 group and 37 (6.3%) participants in the All 8mg group (20 [6.8%] in the 8q8/3 group and 17 [5.7%] in the 8q8/5 group) (Table 111). None of the IOP increased events were serious or led to discontinuation of study intervention; most were mild or moderate in intensity and recovered without sequela. Severe non-serious IOP increased was reported in 1 participant in the 8q8/3 group. IOP increased was assessed as not related to the study intervention in the majority of participants who experienced such events.

Table 116: Treatment-emergent adverse events: intraocular pressure increased in study eye (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	9 (3.0%)	20 (6.8%)	17 (5.7%)	37 (6.3%)
Eye disorders	4 (1.3%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Ocular hypertension	4 (1.3%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Investigations	5 (1.7%)	16 (5.5%)	15 (5.0%)	31 (5.2%)
Intraocular pressure increased	5 (1.7%)	16 (5.5%)	15 (5.0%)	31 (5.2%)

The proportions of participants meeting IOP criteria were generally low in all treatment groups but slightly higher in the All 8mg group compared to the 2q4 group for all criteria except for the most clinically relevant IOP assessment of ≥35 mmHg (pre- or post-dose), for which the incidences were balanced (1.0% All 8mg group vs. 0.3% 2q4 group) (Table 112) . No relevant mean or median changes from baseline to Week 36, or relevant differences across the treatment groups were observed in the analysis of the pre-injection IOP data.

Of note, the proportion of participants with Paracentesis in the study eye by Week 36 was low and similar across the treatment groups (0.7% vs 1.0% in the 2q4 and All 8mg groups, respectively), as shown in a post-hoc analysis.

Table 117: Number of participants meeting intraocular pressure criteria at any visit through week 36- study eye (safety analysis set)

	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Participants with ≥10 mmHg increase in pre-dose IOP from baseline	4 (1.3%)	13 (4.4%)	11 (3.7%)	24 (4.1%)
Participants with pre-dose IOP >21 mmHg	19 (6.3%)	34 (11.6%)	41 (13.8%)	75 (12.7%)
Participants with pre-dose IOP ≥25 mmHg	5 (1.7%)	11 (3.8%)	12 (4.0%)	23 (3.9%)
Participants with pre- or post-dose IOP ≥35 mmHg	1 (0.3%)	3 (1.0%)	3 (1.0%)	6 (1.0%)

Up to week 64, no relevant mean or median changes from baseline to Week 64 or relevant differences across the treatment groups were observed in the analysis of the pre-injection IOP data.

The proportions of participants meeting IOP criteria were generally low in all treatment groups but numerically higher in the All 8mg group compared to the 2q4 group for all criteria except for the IOP assessment of ≥35 mmHg (pre- or post-dose), the parameter that is most clinically relevant, for which the incidences were balanced between the All 8mg group (1.2%) and the 2q4 group (0.7%).

Table 118: Number of participants meeting intraocular pressure criteria at any visit through Week 64 - study eye (safety analysis set)

	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
≥10 mmHg increase in pre-dose IOP from baseline	8 (2.7%)	19 (6.5%)	13 (4.4%)	32 (5.4%)
Pre-dose IOP >21 mmHg	25 (8.3%)	49 (16.7%)	47 (15.8%)	96 (16.2%)
Pre-dose IOP ≥25 mmHg	9 (3.0%)	16 (5.5%)	17 (5.7%)	33 (5.6%)
Pre- or post-dose IOP ≥35 mmHg	2 (0.7%)	3 (1.0%)	4 (1.3%)	7 (1.2%)

Clinically relevant changes in IOP values (in both eyes) were reported as ocular TEAEs under the SOC Investigations and included Intraocular pressure decreased, Intraocular pressure increased, and Intraocular pressure test abnormal.

TEAEs of IOP increased in the study eye were reported in higher proportions in all 8 mg (6.3% vs 3.0% in 2q4 group). None of the events were serious or lead to study intervention discontinuation. Most of the events were mild (3.0% in 2q4 group and 4.4% in all 8 mg group) and recovered/resolved (1.7% in 2q4 group and 3.7% in all 8 mg group). There was a slightly higher proportion of participants in the All 8 mg group than the 2q4 group for all criteria except for the clinically most relevant IOP assessment of ≥ 35 mm Hg (pre- or post-dose). Proportions of participants with Paracentesis in the study eye by Week 36 was low and similar across the treatment groups.

Up to week 64, proportions of patients with IOP assessment of ≥35 mmHg (pre- or post-dose) was well balanced between the All 8mg group (1.2%) and the 2q4 group (0.7%).

- ***TEAEs related to retinal pigment epithelial tear in the study eye***

TEAEs related to retinal pigment epithelial tear in the study eye was not reported through Week 36.

- ***TEAEs related to retinal detachment or retinal tear in the study eye***

TEAEs related to Retinal detachment or Retinal tear in the study eye were reported in 4 participants in total: Retinal tear in 1 (0.3%) participant in the 8q8/3 group and 2 (0.7%) participants in the 8q8/5 group, and Retinal detachment in 1 (0.3%) participant in the 2q4 group (Table 114).

The Retinal detachment for the participant in the 2q4 group was serious and severe in intensity. It was assessed as unrelated to the study intervention but related to the IVT injection. At the time of this report, the event is resolving. All the Retinal tear events were non-serious and mild in intensity.

Table 119: Treatment-emergent adverse events: Retinal tear / retinal detachment in study eye (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	1 (0.3%)	1 (0.3%)	2 (0.7%)	3 (0.5%)
Eye disorders	1 (0.3%)	1 (0.3%)	2 (0.7%)	3 (0.5%)
Retinal detachment	1 (0.3%)	0	0	0
Retinal tear	0	1 (0.3%)	2 (0.7%)	3 (0.5%)

Retinal tear detachment or Retinal tear were reported in 4 participants; Retinal tear in 1 (0.3%) participant in the 8q8/3 group and 2 (0.7%) participants in the 8q8/5 group, and Retinal detachment in 1 (0.3%) participant in the 2q4 group. The event of Retinal detachment was serious, severe, related to the injection procedure and resolving. Events of Retinal tear were mild, non-serious, recovered/resolved or not recovered/not resolved and one event was assessed as related to injection procedure (in 8q8/3 group).

- ***TEAEs related to ATEs***

Potential ATEs were evaluated by a masked adjudication committee according to criteria formerly applied and published by the Antiplatelet Trialists' Collaboration (APTC). ATEs as defined by the APTC criteria include Nonfatal myocardial infarction, Nonfatal stroke (ischemic or haemorrhagic), or Death resulting from vascular or unknown causes.

Three (1.0%) participants in the 8q8/5 group, 5 (1.7%) participants in the 2q4 group and no participant in the 8q8/3 group reported adjudicated APTC events (Table 115). All events were reported in single participant except for Myocardial infarction (1 participant each in the 8q8/5 group and the 2q4 group).

Table 120: Treatment-emergent adverse events: number of participants with APTC event (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	5 (1.7%)	0	3 (1.0%)	3 (0.5%)
Cardiac disorders	2 (0.7%)	0	1 (0.3%)	1 (0.2%)
Acute myocardial infarction	1 (0.3%)	0	0	0
Myocardial infarction	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Injury, poisoning and procedural complications	0	0	1 (0.3%)	1 (0.2%)
Brain herniation	0	0	1 (0.3%)	1 (0.2%)
Nervous system disorders	3 (1.0%)	0	1 (0.3%)	1 (0.2%)
Cerebellar infarction	1 (0.3%)	0	0	0
Cerebellar stroke	1 (0.3%)	0	0	0
Cerebral infarction	0	0	1 (0.3%)	1 (0.2%)
Cerebrovascular accident	1 (0.3%)	0	0	0
Haemorrhage intracranial	1 (0.3%)	0	0	0
Lacunar infarction	1 (0.3%)	0	0	0

The incidence of TEAEs related to ATEs was low and slightly lower in the All 8mg group (2.2%) than in the 2q4 group (3.7%).

All events were reported in single participants except for Blood creatine phosphokinase increased (2 participants in each of the treatment groups), Coronary artery disease (1 participant in the 8q8/3 and 2 participants in the 2q4 group), Cerebral infarction (1 participant each in the 8q8/5 and 2q4 groups), and Carotid arteriosclerosis (1 participant each in the 8q8/3 and 8q8/5 groups). The events were mostly mild or moderate. Serious TEAEs related to ATEs were reported in 4 (0.7%) participants in the All 8mg group (1 [0.3%] and 3 [1.0%] for the 8q8/3 and 8q8/5 groups, respectively) and 4 (1.3%) participants in the 2q4 group. None of the serious events was assessed to be related to the study intervention and all were resolved or resolving except for an event of severe Myocardial infarction for a participant in the 8q8/5 group, which was not resolved.

Table 121: Treatment-emergent adverse events: Arterial thromboembolic events (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	11 (3.7%)	5 (1.7%)	8 (2.7%)	13 (2.2%)
Cardiac disorders	4 (1.3%)	1 (0.3%)	3 (1.0%)	4 (0.7%)
Acute coronary syndrome	0	0	1 (0.3%)	1 (0.2%)
Acute myocardial infarction	1 (0.3%)	0	0	0
Arteriosclerosis coronary artery	0	0	1 (0.3%)	1 (0.2%)
Coronary artery disease	2 (0.7%)	1 (0.3%)	0	1 (0.2%)
Myocardial infarction	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Investigations	2 (0.7%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Blood creatine phosphokinase increased	2 (0.7%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Nervous system disorders	5 (1.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Carotid arteriosclerosis	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Carotid artery occlusion	1 (0.3%)	0	0	0
Carotid artery stenosis	0	0	1 (0.3%)	1 (0.2%)
Cerebellar infarction	1 (0.3%)	0	0	0
Cerebellar stroke	1 (0.3%)	0	0	0
Cerebral infarction	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Cerebrovascular accident	1 (0.3%)	0	0	0
Cerebrovascular disorder	0	1 (0.3%)	0	1 (0.2%)
Lacunar infarction	1 (0.3%)	0	0	0
Vertebral artery stenosis	0	0	1 (0.3%)	1 (0.2%)
Vascular disorders	0	0	1 (0.3%)	1 (0.2%)
Brachiocephalic arteriosclerosis	0	0	1 (0.3%)	1 (0.2%)

APTC events were reported in 5 participants in 2q4 group and 3 participants in 8q8/5 group. All events were reported in single participant except for Myocardial infarction (1 participant each in the 8q8/5 group and the 2q4 group). Events were mainly mild to moderate in intensity and recovered/resolved. Two

cases had a fatal outcome (Haemorrhage intracranial and Brain herniation). None were assessed as related to study intervention or injection procedure.

TEAEs of ATE were reported in low proportions 3,7% in 2q4 group and 2,2% in all 8 mg arm (2,7% in 8q8/5 and 1,7% in 8q8/3). Events reported in more than 2 participants across treatment arms were Blood creatine phosphokinase increased (2 participants in each of the treatment groups), Coronary artery disease (1 participant in the 8q8/3 and 2 participants in the 2q4 group), Cerebral infarction (1 participant each in the 8q8/5 and 2q4 groups), and Carotid arteriosclerosis (1 participant each in the 8q8/3 and 8q8/5 groups). ATE events were mostly mild in intensity and recovering/resolving or not recovered/not resolved through week 36. TESAE were reported for 4 participants in 2q4 group and 2 participants in all 8 mg group. None of the ATE events was assessed to be related to the study intervention or injection procedure.

- ***TEAEs related to hypertension events***

The incidence of TEAEs related to hypertension was slightly higher in the All 8mg group (8.1%) than in the 2q4 group (4.7%) (Table 117). This is consistent with the imbalance in the incidence of non-ocular medical history of the PT Hypertension, with 61.9% in the All 8mg group compared to 57.5% in the 2q4 group.

Table 122: Treatment-emergent adverse events: Hypertension (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	14 (4.7%)	24 (8.2%)	24 (8.1%)	48 (8.1%)
Cardiac disorders	2 (0.7%)	0	0	0
Hypertensive heart disease	2 (0.7%)	0	0	0
Eye disorders	0	0	1 (0.3%)	1 (0.2%)
Retinopathy hypertensive	0	0	1 (0.3%)	1 (0.2%)
Investigations	3 (1.0%)	5 (1.7%)	4 (1.3%)	9 (1.5%)
Blood pressure diastolic increased	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Blood pressure increased	2 (0.7%)	5 (1.7%)	2 (0.7%)	7 (1.2%)
Blood pressure systolic increased	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Vascular disorders	12 (4.0%)	19 (6.5%)	20 (6.7%)	39 (6.6%)
Essential hypertension	1 (0.3%)	0	0	0
Hypertension	10 (3.3%)	19 (6.5%)	20 (6.7%)	39 (6.6%)
Hypertensive emergency	1 (0.3%)	0	0	0

There was no increase from baseline in mean SBP and DBP through Week 36 (Figure 29 and Figure 30). On the contrary, a mean decrease was observed in all treatment groups through Week 36, ranging between -3.5 mmHg and -4.3 mmHg for SBP and between -1.4 mmHg and -2.2 mmHg for DBP. No relevant differences were seen across the treatment groups.

The proportion of participants with pre-defined treatment-emergent potentially clinically significant values (PCSVs) for SBP or DBP was low, and no notable differences were observed across the treatment groups.

Figure 29: Mean change from baseline in systolic blood pressure (mmHg) through Week 36 (safety analysis set)

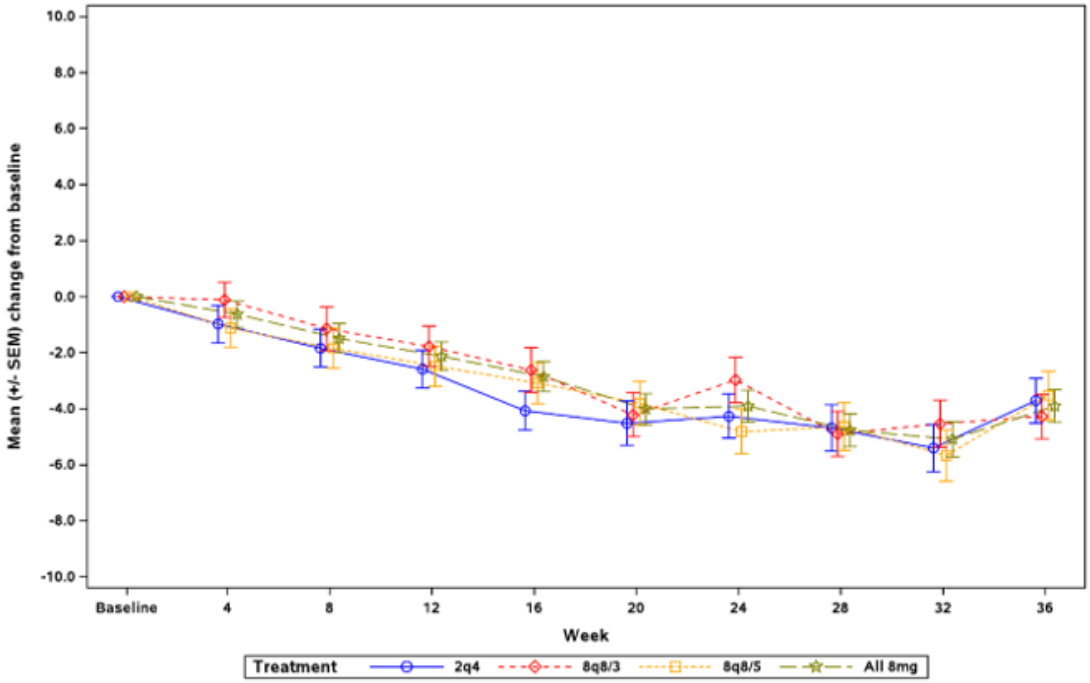
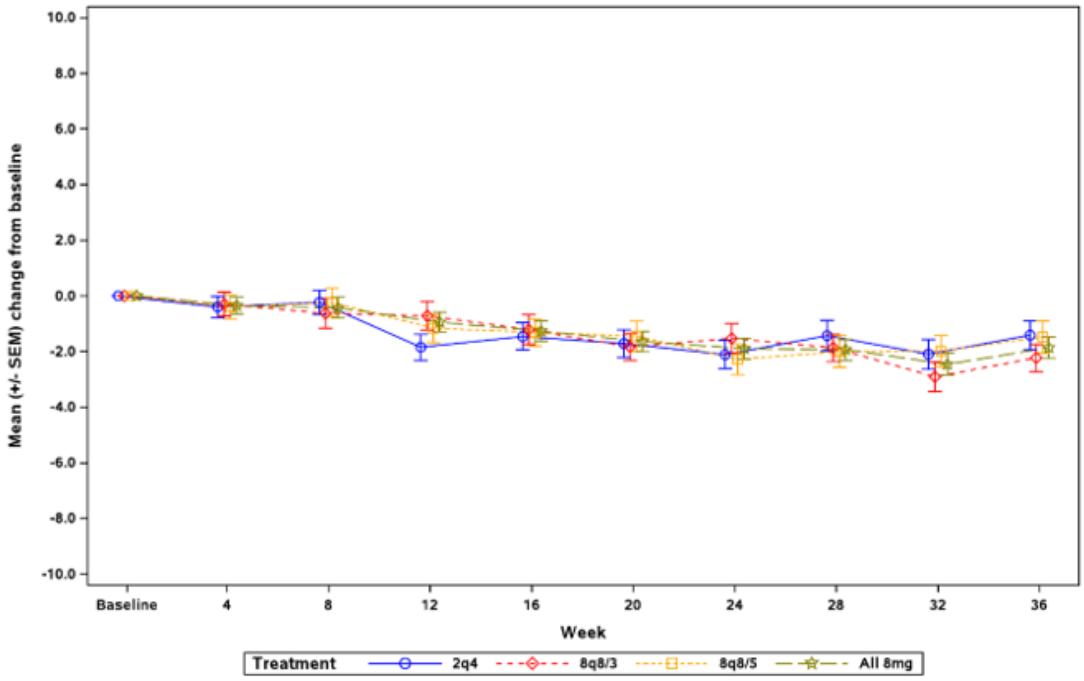


Figure 30: Mean change from baseline in diastolic blood pressure (mmHG) through Week 36 (safety analysis set)



Up to week 64, TEAEs related to hypertension events (MedDRA PTs included are defined in Section 6.3.1 of the SAP in W36 CSR Section 10.1.9) were reported in higher proportion of participants in the All 8mg group (11.3%) than in the 2q4 group (7.0%) (Table 118). This is consistent with the imbalance in incidence of medical history of Hypertension with 65.7% in the All 8mg group compared to 62.1% in the 2q4 group. Overall, approximately 65% of participants in all treatment groups had a medical history of Hypertension.

Table 123: Treatment-emergent adverse events: number of participants with Hypertension by primary system organ class and preferred term (safety analysis set)

Primary system organ class **Preferred term** MedDRA version 28.0	**2q4** N=301 (100%)	**8q8/3** N=293 (100%)	**8q8/5** N=298 (100%)	**All 8mg** N=591 (100%)
Number (%) of participants with ≥ 1 such event	21 (7.0%)	38 (13.0%)	29 (9.7%)	67 (11.3%)
Cardiac disorders	2 (0.7%)	0	0	0
Hypertensive heart disease	2 (0.7%)	0	0	0
Investigations	4 (1.3%)	8 (2.7%)	5 (1.7%)	13 (2.2%)
Blood pressure diastolic increased	1 (0.3%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Blood pressure increased	3 (1.0%)	6 (2.0%)	4 (1.3%)	10 (1.7%)
Blood pressure systolic increased	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Renal and urinary disorders	1 (0.3%)	0	0	0
Hypertensive nephropathy	1 (0.3%)	0	0	0
Vascular disorders	17 (5.6%)	32 (10.9%)	25 (8.4%)	57 (9.6%)
Essential hypertension	1 (0.3%)	0	0	0
Hypertension	15 (5.0%)	31 (10.6%)	25 (8.4%)	56 (9.5%)
Hypertensive crisis	0	1 (0.3%)	0	1 (0.2%)
Hypertensive emergency	1 (0.3%)	0	0	0
Hypertensive urgency	1 (0.3%)	0	0	0

The mean change from baseline in SBP was similar across the treatment groups with numerically small mean decreases in all treatment groups through Week 64, and no relevant differences were seen across the treatment groups. There were no notable differences across the treatment groups for the pre-defined treatment-emergent potentially clinically significant values (PCSVs) for SBP, with a low frequency in all treatment groups (<3.5% for PCSVs decrease, and <10.5% for PCSVs increase). Overall, no consistent trend of changes in SBP was observed during the study.

Table 124: Treatment-emergent potentially clinically significant values for systolic blood pressure at any visit (safety analysis set)

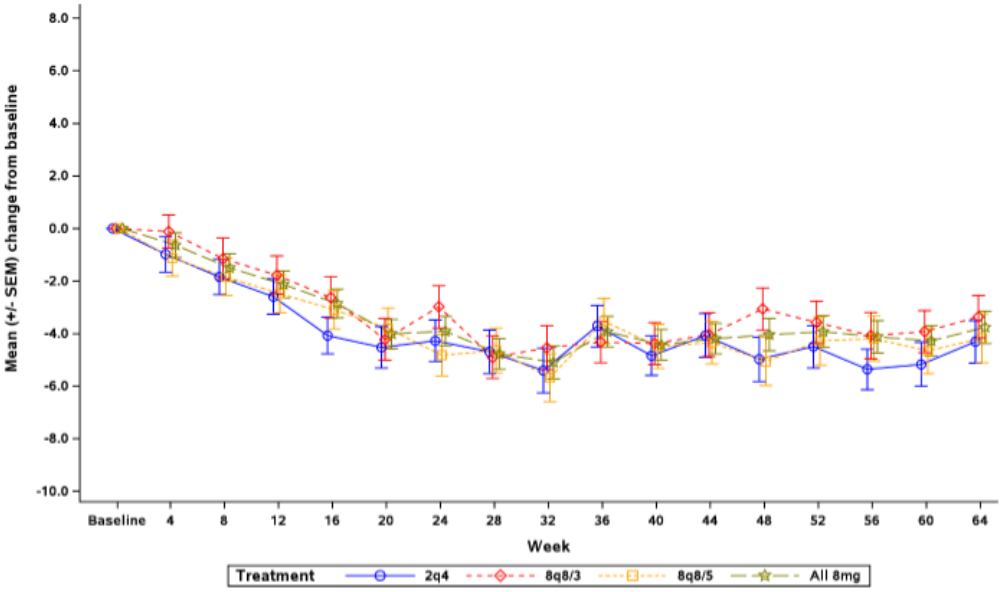
Pre-defined treatment-emergent potentially clinically significant values	**2q4** (N=301) Num/Den(%)	**8q8/3** (N=293) Num/Den(%)	**8q8/5** (N=298) Num/Den(%)	**All 8mg** (N=591) Num/Den(%)
SBP ≤95 mmHg and decrease from baseline ≥20 mmHg	8/299 (2.7%)	7/291 (2.4%)	10/296 (3.4%)	17/587 (2.9%)
SBP ≥160 mmHg and increase from baseline ≥20 mmHg	27/299 (9.0%)	30/291 (10.3%)	22/296 (7.4%)	52/587 (8.9%)

The denominator (Den) represents the number of participants at baseline without an abnormal blood pressure assessment, and at least one valid blood pressure value after start of treatment. Participants with missing or abnormal values at baseline are not included in the denominator.

The numerator (Num) represents the number of participants with at least one abnormal blood pressure assessment after the start of treatment, and without an abnormal blood pressure assessment at baseline.

Participants with at least one treatment-emergent potentially clinically significant value (PCSV) of SBP are displayed.

Figure 31: Mean change from baseline in systolic blood pressure (mmHg) through Week 64 (safety analysis set)



If more than one post-randomization measurement is available for a given visit, the first valid observation will be used.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.
All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals.

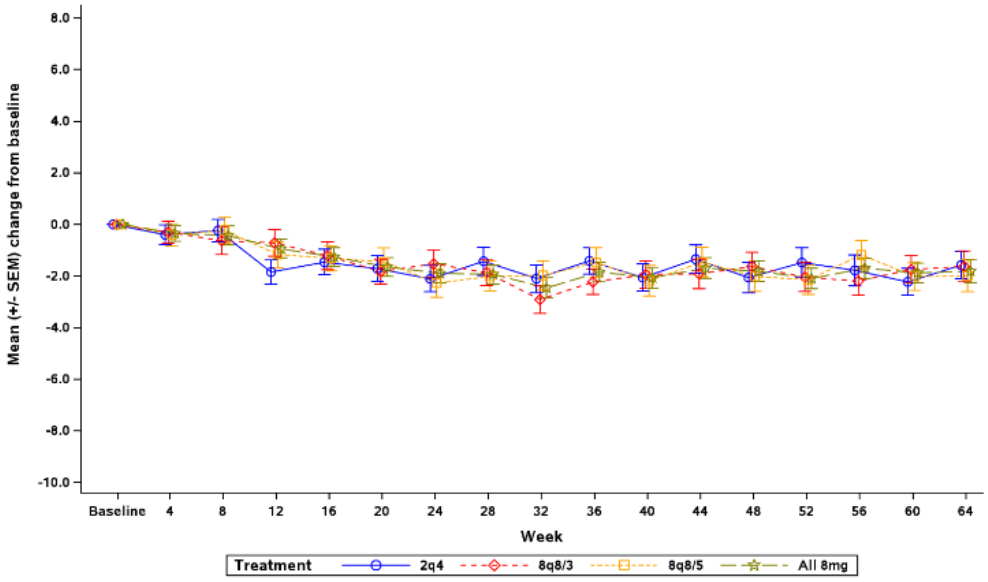
The mean change from baseline in DBP was similar across the treatment groups with numerically slight mean decreases in all treatment groups through Week 64, and no relevant differences were seen across the treatment groups. Pre-defined treatment-emergent PCSVs (increase or decrease) for DBP were only sporadically reported (≤2.7% of participants in any treatment group). Overall, no consistent trend of changes in DBP was observed during the study, although the proportion of participants with DBP ≥110 mmHg and increase from baseline ≥10 mmHg was numerically higher in the All 8mg group compared to the 2q4 group.

Table 125: Treatment-emergent potentially clinically significant values for diastolic blood pressure at any visit (safety analysis set)

Pre-defined treatment-emergent potentially clinically significant values	2q4 (N=301) Num/Den(%)	8q8/3 (N=293) Num/Den(%)	8q8/5 (N=298) Num/Den(%)	All 8mg (N=591) Num/Den(%)
DBP ≤45 mmHg and decrease from baseline ≥10 mmHg	3/299 (1.0%)	1/291 (0.3%)	1/296 (0.3%)	2/587 (0.3%)
DBP ≥110 mmHg and increase from baseline ≥10 mmHg	2/299 (0.7%)	8/291 (2.7%)	6/296 (2.0%)	14/587 (2.4%)

The denominator (Den) represents the number of participants at baseline without an abnormal blood pressure assessment, and at least one valid blood pressure value after start of treatment. Participants with missing or abnormal values at baseline are not included in the denominator.
The numerator (Num) represents the number of participants with at least one abnormal blood pressure assessment after the start of treatment, and without an abnormal blood pressure assessment at baseline.
Participants with at least one treatment-emergent potentially clinically significant value (PCSV) of blood pressure are displayed.

Figure 32: Mean change from baseline in diastolic blood pressure (mmHg) through Week 64 (safety analysis set)



If more than one post-randomization measurement is available for a given visit, the first valid observation will be used.
2q4: Aflibercept 2mg administered every 4 weeks.
8q8/3: Aflibercept 8mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
8q8/5: Aflibercept 8mg administered every 8 weeks, after 5 initial injections at 4-week intervals.
All 8mg: Pooled aflibercept 8mg administered every 8 weeks, after 3 or 5 initial injections at 4-week intervals.

Overall, no clinically relevant changes in BP measurements were observed, although imbalance of AEs of hypertension was observed between the All 8mg group and the 2q4 group (9.5% vs. 5.0%).

Medical history of Hypertension was reported in higher incidence in the all 8 mg group (61.9% vs 57.5% in 2q4 group). Events related to Hypertension were reported in higher proportion in the all 8 mg group (8.1% vs 4.7%). These events were mainly mild (3.3% in 2q4 group and 5.9% in all 8 mg) in intensity and severe in one participants in 2q4 group and 8q8/3 group The reported outcomes were recovered/resolved (2.4% in all 8 mg group vs 1.0% in 2q4 group), recovering/resolving (2.0% in all 8 mg group vs 2.3% in 2q4 group) and not recovered/not resolved (3.6% in all 8 mg group vs 1.3% in 2q4 group) through week 36. TESAE of hypertension were reported in one participants in 2q4 group (severe in intensity, not related to study intervention, not related to protocol-required procedures, not related to intravitreal injection).

Up to week 64, similar tendencies are observed (all 8mg group (11.3%) vs 2q4 group (7.0%)) which is consistent with the imbalance in incidence of medical history of Hypertension with 65.7% in the All 8mg group compared to 62.1% in the 2q4 group.

There was no increase from baseline in mean SBP and DBP through Week 36 and 64. The proportion of participants with pre-defined treatment-emergent potentially clinically significant values (PCSVs) for SBP or DBP was low, and no notable differences were observed across the treatment groups.

- ***TEAEs related to nasal mucosal findings***

The only TEAE related to nasal mucosal findings was Epistaxis, which was reported for 2 (0.7%) participants each in the 8q8/3 and 2q4 groups and 1 (0.3%) participant in the 8q8/5 group (Table 121). One event was serious and moderate in intensity. All other events were non-serious and mild in intensity. None of the events were assessed to be related to the study intervention or the IVT injection procedure, and all resolved without sequela.

Table 126: Treatment-emergent adverse events: Nasal mucosal events (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Respiratory, thoracic and mediastinal disorders	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Epistaxis	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)

Up to week 64, one additional event of epistaxis was reported in the 8q8/3 arm.

Nasal mucosal events consisted of Epistaxis reported in 2 participants each in the 8q8/3 and 2q4 groups (0,7%) and 1 (0.3%) participant in the 8q8/5 group. None were assessed as related to study intervention or injection procedure, all were resolved and one event was moderate and serious in the 2q4 group.

- ***TEAEs related to non-ocular haemorrhages***

TEAEs related to non-ocular haemorrhages was reported in 19 (3.2%) participants in the All 8mg group and 6 (2.0%) participants in the 2q4 group (Table 122). The majority of the events were non-serious, mild in intensity and resolved. Serious TEAEs related to non-ocular hemorrhages were reported in 7 participants (5 [0.8%] in the All 8mg group: 1 [0.3%] and 4 [1.3%] for the 8q8/3 the 8q8/5 groups, respectively, and 2 [0.7%] in the 2q4 group). None of the serious events was assessed to be related to the study intervention. Two serious events led to study intervention withdrawal: an event of severe Haemorrhage intracranial for a participant in the 2q4 group with fatal outcome, and an event of severe Subdural haematoma for a participant in the 8q8/5gorup, which was not resolved. All other serious events were resolved or are resolving at the time of this report and didn't lead to study intervention withdrawal or discontinuation. These serious events were likely associated with concurrent medical conditions and the complications of these conditions associated with an older population. Serious events other than the aforementioned Haemorrhage intracranial and Subdural haematoma are: 2q4 group: Epistaxis and All 8mg groups: Lower gastrointestinal haemorrhage, Blood urine present, Haemarthrosis, and Uterine haemorrhage.

Table 127: Treatment-emergent adverse events: Non-ocular haemorrhage (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	6 (2.0%)	8 (2.7%)	11 (3.7%)	19 (3.2%)
Blood and lymphatic system disorders	0	0	1 (0.3%)	1 (0.2%)
Blood loss anaemia	0	0	1 (0.3%)	1 (0.2%)
Gastrointestinal disorders	0	1 (0.3%)	0	1 (0.2%)
Lower gastrointestinal haemorrhage	0	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	1 (0.3%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Bone contusion	0	1 (0.3%)	0	1 (0.2%)
Contusion	0	1 (0.3%)	2 (0.7%)	3 (0.5%)
Oral contusion	1 (0.3%)	0	0	0
Subdural haematoma	0	0	1 (0.3%)	1 (0.2%)
Investigations	1 (0.3%)	1 (0.3%)	3 (1.0%)	4 (0.7%)
Blood urine present	1 (0.3%)	1 (0.3%)	3 (1.0%)	4 (0.7%)
Musculoskeletal and connective tissue disorders	0	0	1 (0.3%)	1 (0.2%)
Haemarthrosis	0	0	1 (0.3%)	1 (0.2%)
Nervous system disorders	1 (0.3%)	0	0	0
Haemorrhage intracranial	1 (0.3%)	0	0	0
Renal and urinary disorders	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Haematuria	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Reproductive system and breast disorders	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Heavy menstrual bleeding	0	1 (0.3%)	0	1 (0.2%)
Uterine haemorrhage	0	0	1 (0.3%)	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Epistaxis	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Vascular disorders	2 (0.7%)	0	0	0
Scalp haematoma	1 (0.3%)	0	0	0
Vein rupture	1 (0.3%)	0	0	0

TEAEs of non-ocular haemorrhage were reported in 3.2% in All 8 mg group and 2.0% in 2q4 group. These events were mainly mild in intensity (1.3% in 2q4 and 2.0% in All 8 mg), non-serious and recovered/resolved (1.0% in 2q4 group and 1.9% in all 8 mg). Serious TEAEs of non-ocular haemorrhages were reported in 7 participants in comparable proportions across treatment groups (0.8% in the All 8mg group and 0.7% in the 2q4 group). None were assessed as related to study intervention or injection procedure. Two events lead to study intervention discontinuation: Haemorrhage intracranial (with fatal outcome) in 2q4 group and Subdural haematoma in 8q8/5 group.

- ***TEAEs related to venous thromboembolic events***

The incidence of TEAEs related to venous thromboembolic events was low and balanced between the All 8mg group and the 2q4 group (Table 123). All events were non-serious except for an event of mild Retinal vein occlusion for a participant in the 8q8/5 group. This serious event was assessed as not related to the study intervention and resolved at the time of this report.

Table 128: Treatment-emergent adverse events: Venous thrombo-embolic events (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	4 (1.3%)	4 (1.4%)	7 (2.3%)	11 (1.9%)
Eye disorders	3 (1.0%)	4 (1.4%)	5 (1.7%)	9 (1.5%)
Retinal vein occlusion	3 (1.0%)	4 (1.4%)	5 (1.7%)	9 (1.5%)
Vascular disorders	1 (0.3%)	0	2 (0.7%)	2 (0.3%)
Deep vein thrombosis	1 (0.3%)	0	0	0
Embolism venous	0	0	1 (0.3%)	1 (0.2%)
Thrombophlebitis	0	0	1 (0.3%)	1 (0.2%)

Incidences of VTE events were comparable across treatment groups (1.3% in 2q4 group and 1.9% in all 8 mg group). All events were mild and moderate non-serious except for an event of mild Retinal vein occlusion in 8q8/5 group which was resolved and not related to study intervention or injection procedure.

- ***TEAEs related to hypersensitivity***

The incidence of TEAEs related to hypersensitivity was low in all treatment groups (Table 124). All events were mild or moderate in intensity, and all were non-serious except for an event of moderate Anaphylactic reaction for a participant in the 8q8/3 group. This serious event was in the context of a rituximab infusion for rheumatoid arthritis; it was assessed as not related to the study intervention and resolved at the time of this report.

Table 129: Treatment-emergent adverse events: Hypersensitivity (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	2 (0.7%)	5 (1.7%)	4 (1.3%)	9 (1.5%)
Eye disorders	1 (0.3%)	2 (0.7%)	0	2 (0.3%)
Conjunctival oedema	1 (0.3%)	0	0	0
Eye swelling	0	1 (0.3%)	0	1 (0.2%)
Swelling of eyelid	0	1 (0.3%)	0	1 (0.2%)
Immune system disorders	0	1 (0.3%)	0	1 (0.2%)
Anaphylactic reaction	0	1 (0.3%)	0	1 (0.2%)
Skin and subcutaneous tissue disorders	1 (0.3%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Pruritus	0	2 (0.7%)	0	2 (0.3%)
Rash	0	0	2 (0.7%)	2 (0.3%)
Urticaria	1 (0.3%)	0	2 (0.7%)	2 (0.3%)

TEAEs of hypersensitivity were reported in low proportions 0.7% in 2q4 group and 1.5% in all 8 mg group. All events were mild or moderate and were mainly recovered/resolved. One TESAE occurred of moderate event of Anaphylactic reaction in 8q8/3 group which was assessed as not related to study intervention and resolved. One recovered mild non-serious event of rash was assessed as related to study intervention.

Laboratory findings

- **Clinical laboratory evaluations through Week 36**

For hematology and clinical chemistry, there was no evidence of clinically meaningful differences among treatment groups in high or low laboratory abnormalities or pre-defined selected laboratory abnormalities.

For urinalysis, high protein/creatinine (mg/mmol creatinine) values were reported in 10.0% of participants in the All 8mg group and 13.8% of participants in the 2q4. In general, there was no evidence of clinically meaningful differences in high or low urinalysis laboratory abnormalities among treatment groups.

- **Vital signs, physical findings, ECGs and other observations related to safety through Week 36**

There were no clinically meaningful findings in vital signs, physical examinations, ECGs, or other observations related to safety in this study. No significant trends were noted. No pregnancy was reported.

Adverse drug reactions

Overall, all ADRs listed for commercially available 2 mg aflibercept are also considered ADRs for HD aflibercept, although not all 2 mg ADR were observed through Week 36 of the QUASAR study. Based on the review of all available HD aflibercept safety data, no new ADR was identified. On review of safety data from QUASAR through Week 36, there was no meaningful difference in the incidence and nature of events reported across the All 8mg and 2q4 treatment groups.

Based on the 36 Weeks data, no new ADRs are proposed for inclusion. There was no meaningful difference in the incidence and nature of events reported across the All 8mg and 2q4 treatment groups. Frequencies of ADRs in section 4.8 were updated for Corneal abrasion, retinal degeneration and Lenticular opacities (all Uncommon) and the ADRs Blindness and Endophthalmitis were added from the text below regarding ADRs of Eylea 40 mg/mL considered as expected for Eylea 114.3 mg/mL to table I.

These changes are endorsed.

Safety in special populations

Intrinsic factors

Ocular TEAEs in the study eye and non-ocular TEAEs reported in the study through Week 36 were also analyzed by the following subgroups: age, sex, race, ethnicity, baseline BCVA, baseline CST, medical history of hypertension, diabetes, cerebrovascular disease, ischemic heart disease, renal impairment and hepatic impairment and geographic region.

The results of the subgroup analyses of ocular TEAEs in the study eye and non-ocular TEAEs through Week 36 by the predefined subgroups were generally similar to those in the entire study population and did not suggest clinically relevant differences among the treatment groups.

Numerical differences across the treatment groups that were occasionally observed within the subgroups, for example the age subgroup must be interpreted with caution in view of the smaller subgroup sample sizes.

Subgroup analysis showed no clinically relevant differences among treatment group.

Extrinsic factors

Extrinsic factor of interest was bilateral treatment. However, only few participants received bilateral treatment (10 [1.7%] participants in the All 8mg group and 9 [3.0%] participants in the 2q4 group). No pattern of clinically meaningful differences could be observed from the review of safety data in participants treated bilaterally.

Drug interactions

No drug interaction studies were conducted with HD aflibercept.

Use in pregnancy and Lactation

No pregnancy was reported in clinical studies investigating HD aflibercept. Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 4 months after the last intravitreal injection of HD aflibercept.

- ***Overdose***

For QUASAR, AE tables (PT 'overdose'), protocol deviations as well as treatment information on study drug administration were reviewed. No participant received an overdose of study drug in the study eye in the QUASAR study.

- ***Drug abuse***

The method of aflibercept administration is not conducive to drug abuse as it is not prescribed for self-administration and is only administered by qualified health care professionals. Aflibercept is also too large a molecule to cross the blood-brain barrier, thereby limiting any possibility for centrally mediated effects associated with drug abuse.

- ***Withdrawal and Rebound***

So far there is no evidence for rebound phenomenon after discontinuation or withdrawal of aflibercept 2 or 8 mg. However, discontinuation may lead to progression of the underlying disease resulting in impaired visual acuity.

- ***Effects on ability to drive or operate machinery or impairment of mental ability***

Injection with aflibercept has a limited influence on the immediate ability to drive and use heavy machinery due to possible temporary visual disturbances associated either with the intravitreal injection or the eye examination. Patients should not drive or use machines until their visual function has recovered sufficiently. Similarly, when treatment results in visual acuity gains, patients should continue to use caution until visual function has improved sufficiently.

- ***Post-marketing data***

The post-marketing safety profile of 2 mg and 8 mg aflibercept is continuously monitored.

A new ADR of scleritis was identified in the post-marketing data following the IVT injection of 2 mg aflibercept. Scleritis is considered a potentially injection-related reaction and is added as new ADR to the Eylea 40 mg/mL and Eylea 114.3 mg/mL label.

As of 07 January 2025, no new post-marketing safety signal was confirmed for 8 mg aflibercept. The benefit-risk profile of aflibercept across all authorized indications remains favourable.

No new signal was identified from post-marketing data. The next PSUSA for Aflibercept PSUSA/00010020/202511 is expected for mid-2026.

Q4 dosing: safety data

The currently approved label for HD aflibercept in the indications nAMD and DME specifies that injection intervals during maintenance should not be shorter than 2 months, after 3 consecutive monthly doses. To allow a more intense treatment for patients in need the Applicant presents safety data to support the proposed lower limit of 4 weeks (Q4). It is proposed to allow dosing as frequent as Q4 during the maintenance phase for the approved indications of nAMD and DME, as is proposed for the new indication of RVO. The safety data presented below are based on all participants who entered the study.

- **Safety data during the initial monthly dosing period in nAMD (PULSAR), DME (PHOTON), and RVO (QUASAR)**

To further support the safety conclusion of Q4 dosing, safety data during the initial monthly dosing period (Q4) was reviewed in the PULSAR, PHOTON, and QUASAR studies. All treatment groups in these studies received active monthly injections at Day 1, Week 4 and Week 8. The AE profile was compared between aflibercept 2 mg and HD aflibercept treated participants during this period from baseline through Week 12. The review included ocular TEAEs and non-ocular TEAEs for each study.

The Applicantprovided discussion on the ocular and non-ocular TEAEs by SOC and PT, in particular safety topics, for which occurred from day 1 through Week 12 (before the 4th injection) for all three studies.

In the RSI, the Applicant provided relatedness, seriousness and intensity for ocular and non-ocular TEAEs which were recorded during initial monthly dosing phases of PULSAR (AMD), PHOTON (DME) and QUASAR (RVO). These results are included further in the evaluation.

- ***nAMD PULSAR***

<u>Safety analysis of Q4 dosing during the treatment initiation phase</u>

Safety data during the initial treatment phase (q4, monthly treatment) was reviewed for the 2q8 and the HDq12/16 arms and is described below. It was initially requested by the EMA in initial line extension procedure (EMEA/H/C/002392/X/0084/G) and submitted within the D120 responses.

In the PULSAR study, all study arms (2q8, HDq12, HDq16) received 3 initial injections at 4-week intervals (Day 1, Week 4, Week 8).

Thus, all treatment arms in PULSAR received active monthly injections at Day 1, Week 4 and Week 8. The safety data for review was therefore restricted to the time from first injection through Week 12 (before the Week 12 injection) to allow for an additional 4-week observation time after the 3rd dose at Week 8.

As stipulated by the protocol design during the treatment initiation phase through Week 12 the number of injections per patient was identical for HDq12 and HDq16 which means that all HD patients had the same monthly exposure to 8 mg aflibercept.

The AE profile was compared between 2 mg and 8 mg aflibercept treated patients during the treatment initiation phase. The review included ocular TEAEs, non-ocular TEAEs and data for specific safety topics.

Eylea 8 mg was indicated by now in DME and nAMD at the posology of 1 injection per month for 3 consecutive doses then injection intervals may then be extended up to every 4 months (Q16) followed by every 5 months (Q20) such as with a treat-and-extend dosing regimen, while maintaining stable visual and/or anatomic outcomes. The shortest interval between 2 injections is 2 months (Q8) in the maintenance phase and the Applicant submitted this variation to provide safety data in support of shortening to Q4 interval during the maintenance phase.

The safety analysis consists of safety data from day 1 to Week 12 of the initiation phase for PULSAR in 2q8 arm and all HD group. The exposure is described in Efficacy section. Overall, in PULSAR 672 participants with nAMD received a total of 2,001 HD aflibercept injections at Q4 intervals with a mean of 3 injections per participant.

Ocular TEAEs during treatment initiation (through Week 12) PULSAR

In the PULSAR study, the overall frequency of patients with ocular TEAEs in the study eye was low and similar during the treatment initiation phase for 2 mg and 8 mg treated patients (2q8: 17.3%, HDq12: 18.8%, HDq16: 17.5%, all HD: 18.1%), see Table 125.

The majority of ocular events was reported for single patients in the individual arms and no numerically relevant difference was observed between 8 mg and 2 mg treated patients.

Events that were reported in more than 2 patients in the HD arms and where the difference to the 2 mg arm was ≥ 0.5% in both the HD12 and HDq16 arm were retinal haemorrhage, conjunctivitis, IOP increase, and vitreous floaters.

Retinal haemorrhage (RH)

During the treatment initiation phase, RH was less frequently reported for patients treated with 2 mg aflibercept compared to the 8 mg arms (2q8: 0.9%, all HD: 1.8%).

RH is a feature of the underlying AMD disease. As the number of injections for all arms was identical during the loading phase an injection related effect seems implausible. A drug-related effects is not supported. Patients in the HD arms also presented with higher frequencies of RH in the *fellow eye* during the first 12 study weeks with no events in the 2 mg arm (fellow eye incidences up to 12 weeks: 2q8: 0%, HDq12: 0.9%, HDq16: 0.3%, all HD: 0.6%).

Over the 60 weeks PULSAR study duration, more patients in the 2q8 arm experienced RH (4.5%) versus all HD (3.7%). In the PHOTON study no RH was reported for the HDq12 arm during the treatment initiation phase and overall rates were similar between 2 mg and 8 mg treated patients (PHOTON treatment initiation phase: 2q8: 0.6%, all HD: 0.8%). No new safety signal was identified.

Conjunctivitis

During the treatment initiation phase conjunctivitis was less frequently reported for patients treated with 2 mg aflibercept compared to HD patients (2q8: 0%, all HD: 0.7%). Conjunctivitis is a common ocular condition. The injection procedure could theoretically lead to a conjunctivitis. However, as the number of injections was identical for all groups, the imbalance is considered a chance observation. At Week 60, the frequency of conjunctivitis was identical for 2 mg treated and the all HD group (1.5%). Also, no conjunctivitis was reported for the PHOTON study during the treatment initiation phase.

IOP increase

IOP increase was less frequently reported for 2 mg (0.9%) versus 8 mg (all HD: 2.2%) treated patients during the treatment initiation phase.

IOP increase is an acknowledged observation following intravitreal injected medications including Eylea. As 8 mg aflibercept is injected within 70 µl and the 2 mg dose within 50 µl more frequent post-injection IOP elevations may be conceivable with an increase in injection volume. However, while there was a numerical difference of IOP increase during the treatment initiation phase (all events during loading phase were non-serious), at Week 60 the incidences of IOP increases were similar between 2q8 (2.7%) and all HD (3.1%) in the PULSAR study. In the PHOTON study the incidence for IOP increase was similar between 2 mg and 8 mg treated patients during the treatment initiation phase and less frequently seen with 8 mg aflibercept (all HD: 2.4%) compared to 2q8 (4.2%) at Week 60 therefore no consistent observation across the studies for more frequent IOP increases with 70 µl injection was identified. Also, in the PULSAR and the PHOTON study pre-injection IOP measurements remained stable during the initiation phase through Week 60 without indication for sustained IOP elevations.

IOP increase is a listed ADR in the product information for 2 mg/8 mg aflibercept and HCPs are advised to monitor patients for IOP elevation post injection.

Vitreous floaters

Vitreous floaters were less frequently reported for 2 mg (1.8%) versus all HD (HDq12: 0.9%, HDq16: 3.0%, all HD: 1.9%) during the treatment initiation phase. Vitreous floater is an acknowledged and listed ADR of 2/8 mg Eylea. However, the overall difference between 2 mg and all HD was minor and driven by the HDq16 arm. The HDq12 arm had a lower incidence (0.9%) compared to the 2q8 arm (1.8%), therefore, the differences are not consistent for HD and regarded as chance observation.

Table 130: PULSAR: Ocular TEAEs of study eye during loading phase in >1 participants in any treatment group (SAF)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Number (%) of subjects with ≥ 1such event	**58 (17.3%)**	**63 (18.8%)**	**59 (17.5%)**	**122 (18.1%)**
Eye disorders	49 (14.6%)	50 (14.9%)	47 (13.9%)	97 (14.4%)
Cataract	2 (0.6%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Conjunctival haemorrhage	2 (0.6%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
Conjunctivitis allergic	0	2 (0.6%)	0	2 (0.3%)
Detachment of macular retinal pigment epithelium	3 (0.9%)	0	0	0
Dry eye	3 (0.9%)	2 (0.6%)	0	2 (0.3%)
Eye pain	1 (0.3%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Eye pruritus	0	2 (0.6%)	0	2 (0.3%)
Macular fibrosis	4 (1.2%)	0	1 (0.3%)	1 (0.1%)
Ocular discomfort	2 (0.6%)	0	0	0
Ocular hypertension	0	1 (0.3%)	2 (0.6%)	3 (0.4%)
Photophobia	0	0	2 (0.6%)	2 (0.3%)
Punctate keratitis	3 (0.9%)	0	1 (0.3%)	1 (0.1%)
Retinal haemorrhage	3 (0.9%)	6 (1.8%)	6 (1.8%)	12 (1.8%)
Retinal pigment epithelial tear	3 (0.9%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Subretinal fibrosis	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Subretinal fluid	4 (1.2%)	0	1 (0.3%)	1 (0.1%)
Visual acuity reduced	7 (2.1%)	4 (1.2%)	6 (1.8%)	10 (1.5%)
Vitreous detachment	2 (0.6%)	3 (0.9%)	3 (0.9%)	6 (0.9%)
Vitreous floaters	6 (1.8%)	3 (0.9%)	10 (3.0%)	13 (1.9%)
General disorders and administration site conditions	10 (3.0%)	4 (1.2%)	5 (1.5%)	9 (1.3%)
Injection site haemorrhage	0	0	2 (0.6%)	2 (0.3%)
Injection site pain	2 (0.6%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Sensation of foreign body	7 (2.1%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Infections and infestations	0	4 (1.2%)	3 (0.9%)	7 (1.0%)
Conjunctivitis	0	2 (0.6%)	3 (0.9%)	5 (0.7%)
Hordeolum	0	2 (0.6%)	0	2 (0.3%)
Investigations	3 (0.9%)	11 (3.3%)	6 (1.8%)	17 (2.5%)
Intraocular pressure increased	3 (0.9%)	9 (2.7%)	6 (1.8%)	15 (2.2%)

MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAEs = treatment-emergent adverse events
See Definition of Terms for treatment arms description.

Ocular safety topics during treatment initiation (through Week 12) PULSAR

The reviewed ocular safety topics included TEAE groupings for cataract, IOP increase, retinal detachment/tear, RPE tear, and intraocular inflammation. Overall, the incidences for these topics during the treatment initiation phase was low in all groups. Except for IOP increase (discussed above), the frequencies were similar between 2 mg and 8 mg treated patients and no safety concern was identified.

Table 131: PULSAR: Ocular treatment-emergent safety topics during loading phase from baseline to Week12 visit (before potential injection) (TEAE groupings, SAF)

Safety topic MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Cataract, study eye	2 (0.6%)	3 (0.9%)	3 (0.9%)	6 (0.9%)
Intraocular pressure increased, study eye	3 (0.9%)	9 (2.7%)	8 (2.4%)	17 (2.5%)
Retinal pigment epithelial tear, study eye	3 (0.9%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Intraocular Inflammation (IOI), study eye	0	2 (0.6%)	0	2 (0.3%)
Retinal tear/detachment, study eye	0	0	0	0

MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAE = treatment-emergent adverse event
See Definition of Terms for treatment arms description.

Overall, no new safety concern was identified upon review of ocular safety data during the loading phase of the PULSAR study.

In PULSAR, ocular TEAEs occurred in comparable proportions between all HD group (18.1%) and 2q8 (17.3%). Events reported in more than 2 participants during the initiation phase in the all HD group and with a ≥ 0.5% difference to 2q8 in both the HD12 and HDq16 arms were retinal haemorrhage (2q8: 0.9%, all HD: 1.8 % in the study eye and 0% 2q8 and 0.6% in all HD), conjunctivitis (2q8: 0%, all HD: 0.7%), IOP increase (2q8: 0.9%, all HD: 1.5%), and vitreous floaters (2q8: 1.8%, all HD: 1.9%). These events are either listed in the SmPC of Eylea or common ocular condition.

Ocular study drug related TEAEs occurring during the initial monthly dosing phase were reported in higher proportion in all HD group (2,2% vs 0,9% in 2q8). Study drug related ocular TEAEs were all observed in less than 1% of the subjects and reported mostly in single participants except retinal haemorrhage and retinal pigment epithelial tear which are known common AEs of Aflibercept. Ocular serious TEAEs were reported in similar proportions (0.3% 2q8, one case of retinal haemorrhage vs 0.3% All HD, 2 events in HDq16, retinal haemorrhage and angle closure glaucoma). Ocular TEAEs were mostly mild (14.3% vs 13.7%, 2q8 vs All HD) to moderate (2.7% vs 4.3%, 2q8 vs All HD) in intensity and severe Ocular TEAEs were retinal haemorrhage reported once in 2q8 and HDq16.

Regarding ocular safety topics through week 12, comparable frequencies were observed for cataract (0,6% in 2q8 and 0,9% in all HD) and retinal pigment epithelial tear (0,9% in 2q8 and 1,3% in all HD). For IOP increase (2q8: 0,9%, all HD: 1,5%), all events occurring were all non-serious and without sustained IOP elevations. As 8 mg aflibercept is injected within 70 µl and the 2 mg dose within 50 µl, higher frequency of IOP increase may be expected however study pre-injection IOP measurements remained stable during the initiation phase.

The incidence rates for safety topics assessed as study drug related were low and similar between patients treated with 2 mg and those treated with 8 mg treated. Serious events were low (less than 1%) and similar in range. Events were mostly mild to moderate and severe events were low and similar between 2 mg and 8 mg treated patients.

No safety concern is raised, reported ocular TEAEs in the study eye during the initiation phase are in line with the safety profile of Eylea.

Non-ocular events during treatment initiation (through Week 12) PULSAR

In PULSAR, incidences of non-ocular TEAEs in the 2q8 arm (16.7%) were numerically lower than those in the HD arms (22.1%). As in PHOTON the incidences of the 2q8 arm were higher (23.4%) and similar to ranges of the HD arms (all HD: 24.4%) it may be assumed that the difference observed in PULSAR is driven by the rather low rats in 2q8 than an 8mg related treatment effect.

The non-ocular AE profile and systemic safety topics of the PULSAR study were reviewed and did not reveal a new safety concern.

For most of the SOCs the incidences were similar between the HD and the 2mg arm during the treatment initiation phase. Some incidences in the SOCs were higher in the 2q8 arm during the treatment initiation phase versus 8 mg treated patients (e.g., Blood and lymphatic system disorders, Hepatobiliary disorder, Investigations and Metabolism and nutrition disorders).

SOCs with a difference of > 1% and higher in the HD arms compared to 2q8 were the following: Infections and infestations and Vascular disorders.

SOC Infections and infestations: The majority of PTs in this SOC were reported for single patients only. Events reported for more than 1 patient and higher in the HD arms were Pulpitis dental (2 patients in HDq12, none in 2q8 and HDq16), Upper respiratory tract infection (3 patients in HDq12, none in 2q8 and HDq16), and Urinary tract infection (5 patients in HDq16, 1 each in HDq12 and 2q8). These events are not known to be related to anti-VEGF effect and may be expected in the elderly AMD population.

SOC Vascular disorders: The majority of PTs in this SOC were reported for single patients only. The only event experienced by more than 1 patient was PT Hypertension for which the incidences were similar between the groups (PT Hypertension: 2q8: 1.2%, HDq12: 1.8%, HDq16: 2.1%, all HD: 1.9%). No new safety concern was identified.

Table 132: PULSAR: Non-ocular TEAEs during loading phase from baseline to Week12 visit (before potential injection, SAF)

Primary system organ class MedDRA version 25.0	**2q8** N=336 (100%)	**HDq12** N=335 (100%)	**HDq16** N=338 (100%)	**All HD** N=673 (100%)
Number (%) of subjects with at least one such adverse event	56 (16.7%)	67 (20.0%)	82 (24.3%)	149 (22.1%)
Blood and lymphatic system disorders	2 (0.6%)	0	0	0
Cardiac disorders	5 (1.5%)	4 (1.2%)	6 (1.8%)	10 (1.5%)
Ear and labyrinth disorders	1 (0.3%)	4 (1.2%)	0	4 (0.6%)
Endocrine disorders	0	0	1 (0.3%)	1 (0.1%)
Gastrointestinal disorders	9 (2.7%)	9 (2.7%)	12 (3.6%)	21 (3.1%)
General disorders and administration site conditions	3 (0.9%)	5 (1.5%)	6 (1.8%)	11 (1.6%)
Hepatobiliary disorders	2 (0.6%)	0	0	0
Immune system disorders	0	0	2 (0.6%)	2 (0.3%)
Infections and infestations	11 (3.3%)	12 (3.6%)	21 (6.2%)	33 (4.9%)
Injury, poisoning and procedural complications	4 (1.2%)	4 (1.2%)	5 (1.5%)	9 (1.3%)
Investigations	5 (1.5%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Metabolism and nutrition disorders	6 (1.8%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Musculoskeletal and connective tissue disorders	10 (3.0%)	9 (2.7%)	16 (4.7%)	25 (3.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
Nervous system disorders	8 (2.4%)	12 (3.6%)	6 (1.8%)	18 (2.7%)
Psychiatric disorders	2 (0.6%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Renal and urinary disorders	2 (0.6%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
Reproductive system and breast disorders	2 (0.6%)	0	2 (0.6%)	2 (0.3%)
Respiratory, thoracic and mediastinal disorders	4 (1.2%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Skin and subcutaneous tissue disorders	4 (1.2%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Surgical and medical procedures	0	0	1 (0.3%)	1 (0.1%)
Vascular disorders	4 (1.2%)	8 (2.4%)	9 (2.7%)	17 (2.5%)

MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAEs = treatment-emergent adverse events
See Definition of Terms for treatment arms description.

Systemic safety topics during treatment initiation (through Week 12) PULSAR

In addition to the non-ocular AE profile, systemic safety topic TEAE groupings were reviewed and included non-ocular hemorrhages, hypersensitivity, hypertension, arterial thromboembolic events (ATEs), cardiovascular events, cerebrovascular events, APTC events, and nasal mucosal events, see Table 128 below.

For all systemic safety topics, the incidence between 2 mg and 8 mg treated patients were low and similar in range.

Table 133: PULSAR: Non-ocular treatment-emergent safety topics during loading phase (TEAE groupings, SAF)

Observation period from baseline to Week12 visit (before potential injection).

Safety topic Preferred term MedDRA version 25.0	2q8 N=336 (100%)	HDq12 N=335 (100%)	HDq16 N=338 (100%)	All HD N=673 (100%)
Hypersensitivity	1 (0.3%)	1 (0.3%)	3 (0.9%)	4 (0.6%)
Hypertension	6 (1.8%)	7 (2.1%)	10 (3.0%)	17 (2.5%)
Non-ocular haemorrhage	1 (0.3%)	0	2 (0.6%)	2 (0.3%)
Venous thrombo-embolic events	0	0	1 (0.3%)	1 (0.1%)
Cardiovascular ischemic events	1 (0.3%)	0	2 (0.6%)	2 (0.3%)
Cerebrovascular ischemic events	2 (0.6%)	3 (0.9%)	1 (0.3%)	4 (0.6%)
ATEs	3 (0.9%)	3 (0.9%)	3 (0.9%)	6 (0.9%)
APTC events	3 (0.9%)	1 (0.3%)	0	1 (0.1%)
Nasal mucosal events	0	0	1 (0.3%)	1 (0.1%)

APTC = Antiplatelet Trialists' Collaboration, ATEs = arterial thromboembolic events, MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAEs = treatment-emergent adverse events
See Definition of Terms for treatment arms description.

Overall, the review of non-ocular AEs and systemic safety topics during the treatment initiation phase in the PULSAR study did not reveal a new safety concern.

The safety profile during the treatment initiation phase was similar between 2 mg and 8 mg, the overall safety profile of the population treated in the PULSAR studies is in line with the ADR profile of 8 mg aflibercept. No new safety concerns were identified.

Non-ocular TEAEs were reported in higher proportion in the HD arms (22.1%) than in 2q8 arm (16.7%). The SOC "Infection and Infestations" and "Vascular disorders" were more reported in the HD arms with a difference of >1% compared to 2q8, respectively 4.9% vs 3.3% and 2.5% vs 1.2%. For both SOCs, majority of the PT were reported in single participants except Pulpitis dental, Upper respiratory tract infection, Urinary tract infection which may be expected in the elderly population. For the SOC "Vascular disorders", the most reported PT was Hypertension which was reported in similar proportions through Week 12 (1,8% in 2q8 and 2,5% in HD arms). Non-ocular study drug related TEAEs occurring during the initial monthly dosing phase were cerebrovascular accident (2q8) and pulmonary embolism (HDq16). Serious non-ocular TEAEs were reported mostly in single participants and in total in 8 participants [2.4%] in the HDq12 group, 12 participants [3.6%] in the HDq16 group and 14 participants [4.2%] in the 2q8 group. Non-ocular TEAEs were mostly mild (10.1% vs 14.4%, 2q8 vs All HD) to moderate (3.9% vs 6.7%, 2q8 vs All HD) in intensity and severe non-ocular TEAEs were reported in single participants (9 [2.7%] vs 7 [1.0%], 2q8 vs All HD). The majority of the patient recovered or recovering and comparable proportions of patient not recovered were reported in both 2q8 and all HD group (1.5% vs 1.8%).

Regarding systemic safety topics, the incidence between 2 mg and 8 mg treated patients were low and comparable (Hypersensitivity 0.6% in HD arms and 0.3% in 2q8 arm; Hypertension 2.5% in HD arms and 1.8% in 2q8 arm; Non ocular haemorrhage 0.3% in both HD and 2q8 arms; Cardiovascular ischemic events 0.3% in both HD and 2q8 arms; Cerebrovascular ischemic events 0.6% in both HD and 2q8 arms; VTE 0.1% in HD arms and 0% in 2q8 arms; ATEs 0.9% in both HD and 2q8 arms; APTCs events 0.1% in HD arms and 0.9% in 2q8 arm; Nasal mucosal events 0.1% in HD arms and 0% in 2q8 arm). No safety concerned are raised regarding non-ocular TEAEs.

- ***PHOTON (DME)***

Safety analysis of Q4 dosing during the treatment initiation phase

Safety data during the initial treatment phase (Q4, monthly treatment) was reviewed for the 2q8 and the HDq12/16 arms and is described below. It was initially requested in the initial line extension procedure (EMEA/H/C/002392/X/0084/G) and submitted within the responses.

In the PHOTON study, patients in the 2q8 arm received 5 initial injections at 4-week intervals (Day 1, Week 4, Week 8, Week 12, Week 16), and both HD arms (HDq12 and HDq16) received 3 initial injections at 4-week intervals (Day 1, Week 4, Week 8).

Thus, all treatment arms in PHOTON received active monthly injections at Day 1, Week 4 and Week 8. The safety data for review was therefore restricted to the time from first injection through Week 12 (before the Week 12 injection) to allow for an additional 4-week observation time after the 3rd dose at Week 8.

As stipulated by the protocol design during the treatment initiation phase through Week 12 the number of injections per patient was identical for HDq12 and HDq16 which means that all HD patients had the same monthly exposure to 8 mg aflibercept.

The AE profile was compared between 2 mg and 8 mg aflibercept treated patients during the treatment initiation phase. The review included ocular TEAEs, non-ocular TEAEs and data for specific safety topics.

The proposed posology for DME in Eylea SmPC is the same as for nAMD. In PHOTON, 491 participants with DME received a total of 1,455 HD aflibercept injections at Q4 intervals with a mean of 3 injections per participant from day 1 though Week 12.

Ocular TEAEs during treatment initiation (through Week 12) PHOTON

The incidences of ocular TEAEs during the treatment initiation phase were numerically lower in the 2q8 arm compared to the 8 mg arms (2q8: 9.6%, all HD: 17.1%), see Table 129.

In the PHOTON study, the incidences in the HD arms during the initiation phase were similar to rates in PULSAR (PULSAR - all HD: 18.1%, PHOTON - all HD: 17.1%) whereas the rate in the 2q8 arm in PHOTON during the treatment initiation period was lower than in PULSAR (PULSAR - 2q8: 17.3%, PHOTON – 2q8: 9.6%). It is considered that the rather low rate in ocular AEs in the 2q8 arm during treatment initiation in the PHOTON study arm may drive the observed differences to the 8 mg arms rather than an 8 mg aflibercept treatment related effect.

Similar to the study eye, TEAEs in the fellow eye showed a higher incidence in the HD arms versus 2q8 which does not support a drug related effect of aflibercept 8 mg in the study eye.

In the PHOTON study the majority of ocular events were reported for single patients in the individual arms and there were no unexpected clusters around specific AEs. Differences between the arms were minor. Events that were reported in more than 2 subjects in the HD arms and where the difference to the 2 mg arm was > 0.5% in both the HD12 and HDq16 arm compared to 2 mg treated patients were cataract/cataract cortical, conjunctival haemorrhage, photopsia, punctate keratitis, and vitreous detachment.

Cataract and cataract cortical are listed ADRs for 8 mg aflibercept and mainly considered injection related complications. As the number of injections were identical for all arms the numerical difference is considered a chance observation. In the PULSAR study cataract were balanced across all arms during the treatment initiation phase and no consistent trend for a potential drug-related increase of cataract across the studies was identified.

Conjunctival haemorrhage is a listed ADR for 8 mg aflibercept as an injection related event and with same numbers of injections during the loading phase the observed numerical difference is not considered associated with an 8 mg related treatment effect. Incidences for conjunctival haemorrhage were

balanced in the PULSAR study and no consistent trend for a potentially drug-related increase of conjunctival hemorrhage across the studies was identified.

Photopsia in the study eye was reported for 3 patients in the HD arm (0.6%) and for none in the 2 mg arm. The distribution and incidences of photopsia in the fellow eye (fellow eye incidence photopsia: 2q8: 0%, all HD: 0.6%) was the same as in the study eye. Therefore, a drug/injection-related association in the study eye is deemed unlikely.

Punctate keratitis is a listed ADR for 8 mg aflibercept and more frequently reported for the study eye in the HD arms versus 2q8 during the treatment initiation phase. The same pattern and similar incidences were observed in the fellow eye during the first 12 weeks with more events in the HD arm versus the 2q8 fellow eye (fellow eye incidences: 2q8: 0%, all HD: 0.8%). In the PULSAR study punctate keratitis was less frequently reported for the HD arms versus 2 mg (2q8: 0.9%, all HD: 0.1%), therefore no consistent trend across the studies was observed during the loading phase.

Vitreous detachment is a listed ADR for 8 mg aflibercept with none reported for 2 mg versus 1.4% in all HD group during the treatment initiation phase. Vitreous detachment is potentially injection related and as the number of injections was the same per patient and arm this observation seems to reflect a chance finding. Also, in the PULSAR study incidences were balanced between the arms during the treatment initiation, thus, no consistent trend was observed across the studies regarding vitreous detachment.

Table 134: PHOTON: Ocular TEAEs of study eye during loading phase from baseline to Week12 visit (before potential injection) in >1 participants in any treatment group (SAF)

Primary system organ class Preferred term MedDRA version 25.0	2q8 N=167 (100%)	HDq12 N=328 (100%)	HDq16 N=163 (100%)	All HD N=491 (100%)
Number (%) of subjects with at least one such adverse event	**16 (9.6%)**	**56 (17.1%)**	**28 (17.2%)**	**84 (17.1%)**
Eye disorders	15 (9.0%)	51 (15.5%)	28 (17.2%)	79 (16.1%)
Cataract	0	2 (0.6%)	2 (1.2%)	4 (0.8%)
Cataract cortical	0	2 (0.6%)	1 (0.6%)	3 (0.6%)
Conjunctival haemorrhage	2 (1.2%)	11 (3.4%)	4 (2.5%)	15 (3.1%)
Corneal erosion	0	0	2 (1.2%)	2 (0.4%)
Eye irritation	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Eye pain	2 (1.2%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
Meibomian gland dysfunction	1 (0.6%)	2 (0.6%)	0	2 (0.4%)
Ocular hypertension	0	2 (0.6%)	0	2 (0.4%)
Photopsia	0	2 (0.6%)	1 (0.6%)	3 (0.6%)
Punctate keratitis	1 (0.6%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
Retinal exudates	2 (1.2%)	0	1 (0.6%)	1 (0.2%)
Retinal haemorrhage	1 (0.6%)	0	4 (2.5%)	4 (0.8%)
Visual acuity reduced	2 (1.2%)	0	0	0
Visual impairment	0	1 (0.3%)	2 (1.2%)	3 (0.6%)
Vitreous detachment	0	5 (1.5%)	2 (1.2%)	7 (1.4%)
Vitreous floaters	3 (1.8%)	8 (2.4%)	1 (0.6%)	9 (1.8%)
Vitreous haemorrhage	1 (0.6%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Investigations	2 (1.2%)	5 (1.5%)	0	5 (1.0%)
Intraocular pressure increased	2 (1.2%)	5 (1.5%)	0	5 (1.0%)

MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAEs = treatment-emergent adverse events
See Definition of Terms for treatment arms description.

Ocular safety topics during treatment initiation (through Week 12) PHOTON

Except for cataract (see discussion above) for all other safety topics of i.e. intraocular inflammation, retinal detachment/tear, and Retinal pigment epithelial tears the rates were lower/similar between 2 mg and 8 mg arms.

Table 135: PHOTON: Ocular treatment-emergent safety topics during loading phase from baseline to Week 12 visit (before potential injection) (TEAE groupings, SAF)

Safety topic MedDRA version 25.0	**2q8** N=167 (100%)	**HDq12** N=328 (100%)	**HDq16** N=163 (100%)	**All HD** N=491 (100%)
Cataract, study eye	1 (0.6%)	5 (1.5%)	3 (1.8%)	8 (1.6%)
Intraocular pressure increased, study eye	2 (1.2%)	7 (2.1%)	0	7 (1.4%)
Intraocular Inflammation (IOI), study eye	1 (0.6%)	3 (0.9%)	0	3 (0.6%)
Retinal tear / retinal detachment, study eye	0	0	1 (0.6%)	1 (0.2%)
Retinal pigment epithelial tears	0	0	0	0

MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAEs = treatment-emergent adverse events
See Definition of Terms for treatment arms description.

Overall, no new ocular drug-related safety concern was identified based on the review of PHOTON study data.

Ocular TEAEs in the initiation phase were higher in HD groups compared to 2q8 (17.1% vs 9.6%) however this difference may be driven by a lower rate in the 2q8 arm in PHOTON during the treatment initiation than in PULSAR (PULSAR - 2q8: 17.3%, PHOTON – 2q8: 9.6%). Furthermore, ocular TEAEs in the fellow eye also showed a higher incidence in the HD arms versus 2q8.

Events were reported in single participants and difference higher than 0,5% were seen for cataract (0,8% in HD arms vs 0% in 2q8)/cataract cortical (0,6% in HD arms vs 0% in 2q8), conjunctival haemorrhage (3,1% in HD arms vs 1,2% in 2q8), photopsia (0,6% in HD arms vs 0% in 2q8), punctate keratitis (1,2% in HD arms vs 0,6% in 2q8), and vitreous detachment (1,4% in HD arm vs 0% in 2q8). All these events are known ADR or Eylea which are either known as injection related (Vitreous detachment, cataract/cataract cortical and Conjunctival haemorrhage) or also seen in higher proportion in the fellow eye (photopsia and punctuate keratitis). Study drug related ocular TEAEs occurring during the initial monthly dosing phase were reported mostly in single participants except intraocular pressure increased and low proportions (0,6% in 2q8 and 1,2% in all HD group). Serious ocular TEAEs occurred in single participant and were reported in similar proportions (0,6% in 2q8 and 0,4% in all HD group). None were considered related to the study drug. Ocular TEAEs were mild (9.0% vs 15.1%, 2q8 vs All HD) to moderate (0.6% vs 1.4%, 2q8 vs All HD) and severe Ocular TEAEs were reported in low proportions (0% vs 0.6%, 2q8 vs All HD), and in single patients. None were considered related to the study drug.

Ocular safety topics, except for cataract, were reported in comparable proportions between treatment arms (IOP increase 1,4% in HD arms and 1,2% in 2q8 arm; IOI 0,6% in HD arms and 0,6% in 2q8 arm and retinal tear/retinal detachment 0,2% in HD arms and 0% in 2q8). The incidence rates for safety topics assessed as study drug related were low (less than 1%) and were reported in single participants except for IOP increased and IOI. The incidences of serious events between 2 mg and 8 mg treated patients were low and similar in range. Events were mainly mild to moderate and incidence of severe TEAEs were low and comparable between patients treated with 2 mg and 8 mg doses.

No safety concerns are raised. Ocular TEAEs are in line with the known safety profile.

Systemic safety topics during treatment initiation (through Week 12) PHOTON

For most of the non-ocular SOCs, the incidences were similar between the arms or were higher in the 2 mg arm compared to the HD arms.

SOCs with a difference of >1% and higher in the HD arms compared to 2q8 were the following: Gastrointestinal disorders, Infections and infestations, Nervous system disorders, Psychiatric disorders, Renal and urinary disorders and Respiratory, thoracic and mediastinal disorders.

SOC Gastrointestinal disorders: The majority of PTs in this SOC were reported for single patients only. Events experienced by more than 2 patients were PT Food poisoning [2q8: 0%, all HD: 2 (0.4%)], Gastrooesophageal reflux disease [2q8: 0%, all HD: 2 (0.4%)], Nausea [2q8: 0%, all HD: 3 (0.6%)], Vomiting [2q8: 0%, all HD: 2 (0.4%)]. Events are common conditions in the diabetic population and/or not considered related to an intravitreal anti-VEGF effect. No new safety concern was identified.

SOC Infections and infestations: The majority of PTs in this SOC were reported for single patients only. Events experienced by more than 2 patients in the HD arms were COVID-19 [2q8: 2 (1.2%), HDq12: 5 (1.5%), HDq16: 5 (3.1%), all HD: 10 (2.0%)], Herpes zoster [2q8: 0 (0%), HDq12: 1 (0.3%), HDq16: 1 (0.6%), all HD: 2 (0.4%)], Localised infection [2q8: 0 (0%), HDq12: 3 (0.9%), HDq16: 0 (0%), all HD: 3 (0.6%)], Nasopharyngitis [2q8: 0 (0%), HDq12: 4 (1.2%), HDq16: 2 (1.2%), all HD: 6 (1.2%)], Sinusitis [2q8: 0 (0%), HDq12: 1 (0.3%), HDq16: 1 (0.6%), all HD: 2 (0.4%)], and Urinary tract infection [2q8: 1 (0.6%), HDq12: 3 (0.9%), HDq16: 1 (0.6%), all HD: 4 (0.8%)]. These events are not considered anti-VEGF effects and may be expected in the common and/or DME population.

SOC Psychiatric disorders: All events/PTs were reported for single patients only in the HDq12 arm and none in the HDq16 or the 2q8 arm. None of the events was reported in more than 1 patient and there was no cluster around a specific psychiatric disorder in the HD arms.

SOC Renal and urinary disorders: The PT of acute kidney injury [2q8: 0 (0%), HDq12: 4 (1.2%), HDq16: 1 (0.6%), all HD: 5 (1.0%)] and the PT chronic kidney disease [2q8: 0 (0%), HDq12: 2 (0.6%), HDq16: 2 (1.2%), all HD: 4 (0.8%)] were less frequently reported in the 2q8 versus the HD arms, other PTs were reported for single patients only. No similar numerical difference was seen in the PULSAR study during the treatment initiation phase with less/similar incidences in the HD arms compared to the 2q8 arm (SOC Renal and urinary disorders PULSAR: all HD: 0.4%, 2q8: 0.6%). In addition, at Week 60 in the PHOTON study neither patients on a shortened q8 interval (zero events in 8mg treated patients on HDq8 interval versus 19 events in the 2q8 arm) nor in the overall study population at Week 60 a trend for more frequent renal impairments was noted for 8mg treated patients (SOC Renal and urinary disorders at Week 60: all HD: 7.3% versus 7.8% in 2q8). These data do not suggest an 8 mg aflibercept treatment related effect based on a monthly dosing interval.

SOC Respiratory, thoracic and mediastinal disorders: All events/PTs in the HD arms were reported for single patients only. No cluster around a specific respiratory disorder in the HD arms was identified.

Table 136: PHOTON: Non-ocular TEAEs during loading phase (SAF)

Observation period from baseline to Week12 visit (before potential injection).

Primary system organ class MedDRA version 25.0	**2q8** N=167 (100%)	**HDq12** N=328 (100%)	**HDq16** N=163 (100%)	**All HD** N=491 (100%)
Number (%) of subjects with at least one such adverse event	39 (23.4%)	84 (25.6%)	36 (22.1%)	120 (24.4%)
Blood and lymphatic system disorders	2 (1.2%)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Cardiac disorders	5 (3.0%)	10 (3.0%)	1 (0.6%)	11 (2.2%)
Congenital, familial and genetic disorders	1 (0.6%)	0	0	0
Ear and labyrinth disorders	1 (0.6%)	2 (0.6%)	0	2 (0.4%)
Gastrointestinal disorders	2 (1.2%)	9 (2.7%)	3 (1.8%)	12 (2.4%)
General disorders and administration site conditions	1 (0.6%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
Hepatobiliary disorders	0	1 (0.3%)	2 (1.2%)	3 (0.6%)
Immune system disorders	1 (0.6%)	2 (0.6%)	0	2 (0.4%)
Infections and infestations	7 (4.2%)	27 (8.2%)	13 (8.0%)	40 (8.1%)
Injury, poisoning and procedural complications	7 (4.2%)	6 (1.8%)	4 (2.5%)	10 (2.0%)
Investigations	2 (1.2%)	8 (2.4%)	1 (0.6%)	9 (1.8%)
Metabolism and nutrition disorders	5 (3.0%)	9 (2.7%)	7 (4.3%)	16 (3.3%)
Musculoskeletal and connective tissue disorders	7 (4.2%)	5 (1.5%)	2 (1.2%)	7 (1.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Nervous system disorders	3 (1.8%)	10 (3.0%)	7 (4.3%)	17 (3.5%)
Psychiatric disorders	0	7 (2.1%)	0	7 (1.4%)
Renal and urinary disorders	1 (0.6%)	7 (2.1%)	4 (2.5%)	11 (2.2%)
Reproductive system and breast disorders	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Respiratory, thoracic and mediastinal disorders	0	3 (0.9%)	3 (1.8%)	6 (1.2%)
Skin and subcutaneous tissue disorders	3 (1.8%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
Surgical and medical procedures	1 (0.6%)	0	0	0
Vascular disorders	9 (5.4%)	17 (5.2%)	7 (4.3%)	24 (4.9%)

MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAEs = treatment-emergent adverse events
See Definition of Terms for treatment arms description.

In addition to the review of the non-ocular AE profile, systemic safety topics TEAE groupings were reviewed see Table 132 below.

For all systemic safety topics, incidences were low and similar in range between 2 mg and 8 mg treated patients.

Table 137: PHOTON: Non-ocular treatment-emergent safety topics during loading phase (TEAE groupings, SAF)

Observation period from baseline to Week12 visit (before potential injection).

Safety topic MedDRA version 25.0	**2q8** N=167 (100%)	**HDq12** N=328 (100%)	**HDq16** N=163 (100%)	**All HD** N=491 (100%)
Hypersensitivity	1 (0.6%)	3 (0.9%)	0	3 (0.6%)
Hypertension	9 (5.4%)	14 (4.3%)	6 (3.7%)	20 (4.1%)
Non-ocular haemorrhage	1 (0.6%)	3 (0.9%)	0	3 (0.6%)
Cardiovascular ischemic events	3 (1.8%)	4 (1.2%)	1 (0.6%)	5 (1.0%)
Cerebrovascular ischemic events	0	1 (0.3%)	1 (0.6%)	2 (0.4%)
ATEs	3 (1.8%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
APTC events	1 (0.6%)	3 (0.9%)	2 (1.2%)	5 (1.0%)
Nasal mucosal events	0	0	0	0

APTC = Antiplatelet Trialists' Collaboration, ATEs = arterial thromboembolic events, MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAEs = treatment-emergent adverse events
See Definition of Terms for treatment arms description.

Overall, the review of non-ocular AEs and systemic safety topics during the treatment initiation phase in the PHOTON study did not reveal a new safety concern.

The safety profile during the treatment initiation phase was similar between 2 mg and 8 mg, the overall safety profile of the population treated in the PHOTON studies is in line with the ADR profile of 8 mg aflibercept. No new safety concerns were identified.

For non-ocular TEAEs in PHOTON through Week 12, SOC with a difference of > 1% and higher in the HD arms were Gastrointestinal disorders 2,4% in HD arms and 1,2% in 2q8 arm), Infections and infestations (8.2% in HD arms and 4.2% in 2q8 arm), Nervous system disorders (3.5% in HD arms and 1.8% in 2q8 arm), Psychiatric disorders (1,4% in HD arms and 0% in 2q8 arm), Renal and urinary disorders (2.2% in HD arms and 0.6% in 2q8 arm) and Respiratory, thoracic and mediastinal disorders (1.2% in HD arms and 0% in 2q8 arm). In these SOCs, events were reported mostly in single participants or were common conditions in the DME population and/or not considered related to an intravitreal anti-VEGF effect.

Non-ocular safety topics were reported in similar or comparable proportions (Hypersensitivity 0.6% in both HD and 2q8 arm; Hypertension 4.1% in HD arms and 5.4% in 2q8 arm; Non-ocular haemorrhage 0.6% in both HD and 2q8 arms; Cardiovascular ischemic events 1.0% in HD arms and 1.8% in 2q8 arm; Cerebrovascular ischemic events 0.4% in HD arms and 0% in 2q8 arms; ATEs 1.2% in HD arms and 1.8% in 2q8 arms; APTCs events 1.0% in HD arms and 0.6% in 2q8 arm; Nasal mucosal events 0% in both HD and 2q8 arms).

Non-ocular study drug related TEAEs during the initial monthly dosing phase occurred in only one patient (lacunar infarction, mild in intensity, non-serious, patient with underlying risk factors (e.g. diabetes mellitus)). Non-ocular serious TEAEs were more reported in all HD group (3.6% vs 6.3%, 2q8 vs All HD group) but no differences above 1% were seen between SOC. Non-ocular serious TEAEs reported in ≥2 participants in any treatment group were Myocardial infarction (3 [0.6%] patients), COVID-19 (3 [0.6%] patients) and Acute kidney injury (3 [0.6%] patients). None were considered as related to study drug. Non-ocular TEAEs were mainly mild (14.4% vs 13.0%, 2q8 vs All HD) to moderate (6.0% vs 7.1%, 2q8 vs All HD) and severe non-ocular TEAEs were reported in 5 participant [3.0%] vs 21 participants [4.3%], 2q8 vs All HD) and mostly observed in single participants except for myocardial infarction, COVID-19 and acute kidney injury. None were considered related to the study drug.

No safety concerns are raised regarding reported non-ocular TEAEs in PHOTON.

- ***RVO (QUASAR)***

Safety analysis of Q4 dosing during the treatment initiation phase

Safety data during the initial treatment phase (q4, monthly treatment) was reviewed for the 2q4 and the All 8mg arms (8q8/3, 8q8/5) and is described below.

In the QUASAR study, patients in the 2q4 arm received injections at 4-week intervals up to Week 36, in the 8q8/3 arm patients received 3 initial 4-weekly injections and in the 8q8/5 arm patients received 5 initial injections also at 4-week intervals.

Thus, all treatment arms in QUASAR received active monthly injections at Day 1, Week 4 and Week 8. The safety data for review was therefore restricted to the time from first injection through Week 12 (before the Week 12 injection) to allow for an additional 4-week observation time after the 3rd dose at Week 8.

As stipulated by the protocol design during the treatment initiation phase through Week 12 the number of injections per patient was identical for 2q4, 8q8/3 and 8q8/5 which means that all HD patients had the same monthly exposure to 8 mg aflibercept.

The AE profile was compared between 2 mg and All 8 mg aflibercept treated patients during the treatment initiation phase. The review included ocular TEAEs, non-ocular TEAEs and data for specific safety topics.

The posology proposed for RVO is 1 injection per month for 3 consecutive doses than injection intervals may then be extended based on the physician's judgement of visual and/or anatomic outcomes. The interval between 2 injections should not be shorter than 1 month. For the ongoing study QUASAR, participants with RVO treated with HD aflibercept received either 3 or 5 injections at Q4 intervals during the initial monthly dosing phase (8q8/3 or 8q8/5). Through Week 36, a total of 591 participants received a total of 2,470 HD aflibercept injections at Q4 intervals in QUASAR.

Ocular TEAEs during treatment initiation (through Week 12) QUASAR

In the QUASAR study, the overall frequency of patients with ocular TEAEs in the study eye was low and comparable during the treatment initiation phase for 2 mg and All 8 mg treated patients (2q4: 13.6%, 8q8/3: 18.1%, 8q8/5: 15.1%, All 8mg: 16.6%), see Table 133.

The majority of ocular events was reported for single patients in the individual arms and no numerically relevant difference was observed between 8 mg and 2 mg treated patients.

Events that were reported in more than 2 patients in the 8mg arms and where the difference to the 2 mg arm was >0.5% in the All 8mg arm were vitreous detachment and intraocular pressure increased.

Vitreous detachment

Vitreous detachment was not reported for 2 mg and in 4 patients (0.7%) in the All 8mg group during the treatment initiation phase (8q8/3: 0.3%, 8q8/5: 1.0%, all 8mg: 0.7%). Vitreous detachment is an acknowledged and listed ADR of 2/8 mg Eylea. The frequency for 8mg is overall low (0.7%, All 8mg) and similar to the one previously observed in PULSAR and PHOTON study in the AMD and DME indication. No new safety signal was identified.

IOP increase

IOP increase was less frequently reported for 2 mg (0.7%) compared to 8 mg (All 8mg: 3.0%) treated patients during the treatment initiation phase.

IOP increase is an acknowledged observation following intravitreally injected medications including Eylea. As 8 mg aflibercept is injected within 70 µl and the 2 mg dose within 50 µl more frequent post-injection IOP elevations may be conceivable with an increase in injection volume. This numerical difference of IOP increase during the treatment initiation phase (all events during loading phase were non-serious) is not considered as clinically relevant for the following reasons: in the PULSAR and PHOTON studies in AMD and DME indication no such numerical difference was observed between 2mg vs 8mg arms and there is no difference in injection volume used in QUASAR. Also, the pre-injection IOP measurements remained stable during the initiation phase through Week 36 without indication for sustained IOP elevations.

IOP increase is a listed ADR in the product information for 2 mg / 8 mg aflibercept and HCPs are advised to monitor patients for IOP elevation post injection.

Table 138: QUASAR: Ocular TEAEs of study eye during loading phase in >1 participants in any treatment group (SAF)

Primary system organ class Preferred term MedDRA version 27.1	**2q4** N=301 (100%)	**8q8/3** N=293 (100%)	**8q8/5** N=298 (100%)	**All 8mg** N=591 (100%)
Number (%) of participants with at least one such adverse event	**41 (13.6%)**	**53 (18.1%)**	**45 (15.1%)**	**98 (16.6%)**
Eye disorders	35 (11.6%)	42 (14.3%)	35 (11.7%)	77 (13.0%)
Borderline glaucoma	0	2 (0.7%)	0	2 (0.3%)
Cataract	1 (0.3%)	1 (0.3%)	4 (1.3%)	5 (0.8%)
Cataract cortical	0	2 (0.7%)	0	2 (0.3%)
Conjunctival haemorrhage	4 (1.3%)	6 (2.0%)	4 (1.3%)	10 (1.7%)
Dry eye	1 (0.3%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Epiretinal membrane	2 (0.7%)	1 (0.3%)	3 (1.0%)	4 (0.7%)
Eye pain	2 (0.7%)	4 (1.4%)	1 (0.3%)	5 (0.8%)
Macular hole	2 (0.7%)	0	1 (0.3%)	1 (0.2%)
Ocular hypertension	2 (0.7%)	3 (1.0%)	0	3 (0.5%)
Punctate keratitis	3 (1.0%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Retinal exudates	0	1 (0.3%)	2 (0.7%)	3 (0.5%)
Visual acuity reduced	3 (1.0%)	6 (2.0%)	3 (1.0%)	9 (1.5%)
Vitreous detachment	0	1 (0.3%)	3 (1.0%)	4 (0.7%)
Vitreous floaters	2 (0.7%)	3 (1.0%)	0	3 (0.5%)
Vitreous haemorrhage	0	1 (0.3%)	2 (0.7%)	3 (0.5%)
General disorders and administration site conditions	3 (1.0%)	1 (0.3%)	2 (0.7%)	3 (0.5%)
Injection site irritation	1 (0.3%)	0	2 (0.7%)	2 (0.3%)
Infections and infestations	2 (0.7%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Hordeolum	0	0	2 (0.7%)	2 (0.3%)
Injury, poisoning and procedural complications	0	4 (1.4%)	2 (0.7%)	6 (1.0%)
Intra-ocular injection complication	0	3 (1.0%)	0	3 (0.5%)
Investigations	2 (0.7%)	11 (3.8%)	7 (2.3%)	18 (3.0%)
Intraocular pressure increased	2 (0.7%)	11 (3.8%)	7 (2.3%)	18 (3.0%)

MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAEs = treatment-emergent adverse events
See Definition of Terms for treatment arms description.

Ocular safety topics during treatment initiation (through Week 12) QUASAR

The reviewed ocular safety topics included TEAE groupings for cataract, IOP increase, retinal detachment/tear, RPE tear, and intraocular inflammation. Overall, the incidences for these topics during the treatment initiation phase was low in all groups and there were no events pertaining to retinal pigment epithelial tear reported in either group. Except for IOP increase (discussed above) and cataract, the frequencies were similar between 2 mg and 8 mg treated patients and no safety concern was identified. For cataract the numerical difference was <1% for 2mg and All 8 mg and cataract is a known ADR in the product information for 2 mg / 8 mg aflibercept.

Table 139: QUASAR: Ocular treatment-emergent safety topics during loading phase from baseline to Week 12 visit (before potential injection) (TEAE groupings, SAF)

Safety topic MedDRA version 27.1	2q4 N=301 (100%)	2q8/3 N=293 (100%)	2q8/5 N=298 (100%)	All 8mg N=591 (100%)
Cataract, study eye	2 (0.7%)	4 (1.4%)	5 (1.7%)	9 (1.5%)
Intraocular pressure increased, study eye	4 (1.3%)	14 (4.8%)	7 (2.3%)	21 (3.6%)
Retinal pigment epithelial tear, study eye	0	0	0	0
Intraocular Inflammation (IOI), study eye	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Retinal tear/detachment, study eye	1 (0.3%)	0	0	0

MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAE = treatment-emergent adverse event
See Definition of Terms for treatment arms description.

Overall, no new safety concern was identified upon review of ocular safety data during the loading phase of the QUASAR study.

In QUASAR, incidence of ocular TEAEs was slightly higher in HD arms (16.6% vs 13.6% in 2q4 arm). Ocular TEAEs reported through Week 12 in more than 2 participants and with a difference >0.5% were vitreous detachment (0% in 2q4 arm and 0.7% in HD arms) and intraocular pressure increased (1.3% in 2q4 arm and 3.6% in HD arms) which are known ADR of Eylea. All events of IOP increased during the loading phase of QUASAR were non-serious and pre-injection IOP measurements remained stable without indication for sustained IOP elevations. Study drug related ocular TEAE occurring during the initial monthly dosing were reported in low proportions and in single participants except visual acuity reduced (0.7% vs 0.3%, 2q4 vs All 8mg) and intraocular pressure increased (0% vs 1.2%, 2q4 vs All 8mg). A low proportion of patients experienced a serious ocular TEAE (1.3% vs 0.3%, 2q4 vs All 8mg. Ocular TEAEs were mild (9.3% vs 13.5%m, 2q4 vs All 8mg) to moderate (3.3% vs 2.9%, 2q4 vs All 8mg) in intensity and severe events were reported in single participants in 3 (1.0%) patients in the 2q4 group and 1 (0.2%) patient in the All 8mg group. For ocular safety topics (cataract, IOI and retinal tear/detachment), no differences were seen except for IOP increased. Events related to safety topics assessed as study drug related were intraocular pressure increased and hypersensitivity. The incidence of serious TEAEs among patients treated with 2 mg and 8 mg doses was low and similar in range or occurred only in single participants. Events were mostly mild to moderate and severe events were observed in low proportions and in a comparable range between 2 mg and 8 mg treated patients.

No safety concerns were raised regarding ocular TEAEs in QUASAR.

Non-ocular events during treatment initiation (through Week 12) QUASAR

In QUASAR, the incidences of non-ocular TEAEs in the All 8mg group (22.8%) were lower than those in the 2q4 arm (26.6%). For most of the SOCs the incidences were similar between the 8mg and the 2mg arm during the treatment initiation phase.

The only SOC with a difference of > 1% and higher in the All 8mg arm compared to 2q4 was Vascular disorders.

SOC Vascular disorders: The majority of PTs in this SOC were reported for single patients only. The only event experienced by more than 1 patient was PT Hypertension for which the difference in incidence rate was 1.6% (All 8mg vs 2q4). This is consistent with the imbalance in the incidence of non-ocular medical history of PT Hypertension (61.9% in All 8mg group and 57.5% in the 2q4 group). Also, there was no increase from baseline in mean systolic blood pressure and diastolic blood pressure through Week 36. Overall, no new safety concern was identified.

Table 140: QUASAR: Non-ocular TEAEs during loading phase from baseline to Week 12 visit (before potential injection, SAF)

Primary system organ class MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Number (%) of participants with at least one such adverse event	**80 (26.6%)**	**66 (22.5%)**	**69 (23.2%)**	**135 (22.8%)**
Blood and lymphatic system disorders	2 (0.7%)	0	1 (0.3%)	1 (0.2%)
Cardiac disorders	4 (1.3%)	2 (0.7%)	4 (1.3%)	6 (1.0%)
Congenital, familial and genetic disorders	0	1 (0.3%)	0	1 (0.2%)
Ear and labyrinth disorders	0	0	1 (0.3%)	1 (0.2%)
Gastrointestinal disorders	12 (4.0%)	8 (2.7%)	11 (3.7%)	19 (3.2%)
General disorders and administration site conditions	5 (1.7%)	7 (2.4%)	1 (0.3%)	8 (1.4%)
Hepatobiliary disorders	1 (0.3%)	0	4 (1.3%)	4 (0.7%)
Immune system disorders	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Infections and infestations	27 (9.0%)	23 (7.8%)	21 (7.0%)	44 (7.4%)
Injury, poisoning and procedural complications	3 (1.0%)	4 (1.4%)	4 (1.3%)	8 (1.4%)
Investigations	5 (1.7%)	7 (2.4%)	3 (1.0%)	10 (1.7%)
Metabolism and nutrition disorders	5 (1.7%)	1 (0.3%)	12 (4.0%)	13 (2.2%)
Musculoskeletal and connective tissue disorders	9 (3.0%)	5 (1.7%)	6 (2.0%)	11 (1.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.7%)	1 (0.3%)	3 (1.0%)	4 (0.7%)
Nervous system disorders	9 (3.0%)	5 (1.7%)	8 (2.7%)	13 (2.2%)
Psychiatric disorders	2 (0.7%)	2 (0.7%)	0	2 (0.3%)
Renal and urinary disorders	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (0.5%)
Reproductive system and breast disorders	3 (1.0%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Respiratory, thoracic and mediastinal disorders	5 (1.7%)	9 (3.1%)	0	9 (1.5%)
Skin and subcutaneous tissue disorders	3 (1.0%)	3 (1.0%)	3 (1.0%)	6 (1.0%)
Social circumstances	1 (0.3%)	0	0	0
Surgical and medical procedures	0	0	1 (0.3%)	1 (0.2%)
Vascular disorders	9 (3.0%)	11 (3.8%)	16 (5.4%)	27 (4.6%)

MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAEs = treatment-emergent adverse events
See Definition of Terms for treatment arms description.

Systemic safety topics during treatment initiation (through Week 12) QUASAR

In addition to the non-ocular AE profile, systemic safety topic TEAE groupings were reviewed and included non-ocular hemorrhages, hypersensitivity, hypertension, arterial thromboembolic events (ATEs), APTC events and nasal mucosal events, see Table 136 below.

For all systemic safety topics except Hypertension and ATEs, the incidence between 2 mg and 8 mg treated patients were low and similar. For Hypertension (see also further above) the incidence for All 8mg was numerically higher compared to 2q4, whereas for ATEs the incidence was numerically higher in the 2q4 arm compared to All 8mg. However, the differences are < 1.5% and not considered clinically relevant.

Table 141: QUASAR: Non-ocular treatment -emergent safety topics during loading phase (TEAE groupings, SAF)

Observation period from baseline to Week 12 visit (before potential injection).

Safety topic Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Hypersensitivity	1 (0.3%)	1 (0.3%)	2 (0.7%)	3 (0.5%)
Hypertension	10 (3.3%)	14 (4.8%)	14 (4.7%)	28 (4.7%)
Non-ocular haemorrhage	4 (1.3%)	4 (1.4%)	4 (1.3%)	8 (1.4%)
Venous thrombo-embolic events	1 (0.3%)	0	2 (0.7%)	2 (0.3%)
ATEs	4 (1.3%)	0	2 (0.7%)	2 (0.3%)
APTC events	2 (0.7%)	0	2 (0.7%)	2 (0.3%)
Nasal mucosal events	2 (0.7%)	1 (0.3%)	0	1 (0.2%)

APTC = Antiplatelet Trialists' Collaboration, ATEs = arterial thromboembolic events, MedDRA = medical dictionary for regulatory activities, SAF = safety analysis set, TEAE = treatment-emergent adverse event
See Definition of Terms for treatment arms description.

Overall, the review of non-ocular AEs and systemic safety topics during the treatment initiation phase in the QUASAR study did not reveal a new safety concern.

Neither relevant differences nor a consistent trend was observed in the QUASAR study that would indicate a drug-related treatment effect based on a monthly 8 mg aflibercept dosing interval. The safety profile during the treatment initiation phase was similar between 2 mg and 8 mg, the overall safety profile of the population treated in the QUASAR study is in line with the ADR profile of 8 mg aflibercept. No new safety concerns were identified.

This conclusion is further supported by the population PK analyses and the estimated systemic exposure to aflibercept under monthly Q4 dosing over 72 weeks. A continuous Q4 dosing was shown to result in only minor accumulation during the initial dosing phase (median accumulation ratio 1.1) and not in any further accumulation, i.e. systemic exposure increase, of free aflibercept after the 3 initial monthly doses.

In QUASAR, non-ocular TEAEs were reported in lower incidences in the HD groups compared to 2q4 (22,8% vs 26,6%). The SOC Vascular Disorders was more reported in the HD arms (4,6% vs 3,0% in 2q4 arm). All events were reported in single participants except Hypertension (4,7% in HD arms vs 3,3% in 2q4 arm) which may be explained by the imbalance in medical history (61.9% in All 8mg group and 57.5% in the 2q4 group). No increase from baseline in mean systolic blood pressure and diastolic blood pressure was observed through Week 36. Other systemic safety concern (Hypersensitivity, Non-ocular haemorrhage, VTE, ATE, APTC events and Nasal mucosal events) were either comparable between treatment arms or reported in higher incidence in 2q4 arm. Non-ocular TEAEs occurring during the initial monthly dosing phase were related to study drug in only two patients (rash, non-serious, mild intensity recovered with remedial treatment in the 8q8/5 group and headache, non-serious, moderate intensity, related to study drug and protocol required procedure, recovered without remedial treatment in the 8q8/3 group). Serious non-ocular TEAEs were reported in single participants in 11 participants (1.9%) in the All 8mg group and 9 participants (3.0%) in the 2q4 group. Non-ocular TEAEs were mild (16.9% vs 16.4%, 2q4 vs All 8mg) to moderate (8.6% vs 5.1%, 2q4 vs All 8mg) in intensity and severe TEAEs were reported in single participants in similar proportions 1.0% vs 1.4%, 2q4 vs All 8mg.

Discontinuation due to adverse events

- ***Ocular TEAEs in the study eye leading to discontinuation of study intervention***

Ocular TEAEs in the study eye leading to discontinuation of study intervention were reported in 1 (0.3%) participant each in the 8q8/5 group and the 2q4 group (Table 137).

- ***Non-ocular TEAEs leading to discontinuation of study intervention***

Non-ocular TEAEs leading to discontinuation of study intervention were reported in 5 (0.8%) participants in the All 8mg group (2 [0.7%] and 3 [1.0%] for the 8q8/3 and 8q8/5 groups, respectively) and 3 (1.0%) participants in the 2q4 group. No specific safety trend was observed, and all events were reported in single participants (Table 137).

Table 142: TEAEs leading to discontinuation of study intervention (safety analysis set)

Primary system organ class Preferred term MedDRA version 27.1	2q4 N=301 (100%)	8q8/3 N=293 (100%)	8q8/5 N=298 (100%)	All 8mg N=591 (100%)
Ocular TEAEs in the study eye				
Number (%) of participants with at least one such adverse event	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Eye disorders	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Macular hole	1 (0.3%)	0	0	0
Retinal vasculitis	0	0	1 (0.3%)	1 (0.2%)
Non-ocular TEAEs				
Number (%) of participants with at least one such adverse event	3 (1.0%)	2 (0.7%)	3 (1.0%)	5 (0.8%)
Cardiac disorders	0	0	1 (0.3%)	1 (0.2%)
Acute coronary syndrome	0	0	1 (0.3%)	1 (0.2%)
General disorders and administration site conditions	0	0	1 (0.3%)	1 (0.2%)
Chest pain	0	0	1 (0.3%)	1 (0.2%)
Infections and infestations	1 (0.3%)	1 (0.3%)	0	1 (0.2%)
Pneumonia	1 (0.3%)	0	0	0
Sepsis	0	1 (0.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications	0	0	1 (0.3%)	1 (0.2%)
Brain herniation	0	0	1 (0.3%)	1 (0.2%)
Subdural haematoma	0	0	1 (0.3%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.3%)	1 (0.3%)	2 (0.3%)
Oesophageal carcinoma	0	1 (0.3%)	0	1 (0.2%)
Prostate cancer metastatic	0	0	1 (0.3%)	1 (0.2%)
Nervous system disorders	2 (0.7%)	0	0	0
Haemorrhage intracranial	1 (0.3%)	0	0	0
Headache	1 (0.3%)	0	0	0
Vascular disorders	1 (0.3%)	0	0	0
Giant cell arteritis	1 (0.3%)	0	0	0

Ocular TEAEs in the study eye leading to study intervention discontinuation were low 0.3% in 2q4 and 0.2% in All 8 mg group and consisted of Macular hole in 2q4 group (severe, serious, not recovered/not resolved, related to injection procedure) and Retinal vasculitis in 8q8/5 group (moderate, serious, not recovered/not resolved, related to study intervention).

Non-ocular TEAEs leading to study intervention discontinuation were reported in single participants; 5 (0.8%) participants in the All 8mg group (2 [0.7%] and 3 [1.0%] for the 8q8/3 and 8q8/5 groups, respectively) and 3 (1.0%) participants in the 2q4 group.

2.5.1. Discussion on clinical safety

QUASAR study: RVO indication

The high dose of aflibercept (HD, 8 mg or 114.3 mg/mL) has been approved in EU in 2024 (EMEA/H/C/002392/X/0084/G) for the indications nAMD and DME. In this submission, the request for approval of the indication macular oedema secondary to retinal vein occlusion (RVO), which is already approved for Eylea 2 mg, is based on the safety data up to 36 weeks of QUASAR, a randomized, double-masked, active-controlled Phase 3 study comparing 2q4 (Aflibercept 2 mg every 4 weeks until Q32) with 8q8/3 (Aflibercept 8 mg with 3 initial every 4 weeks followed by every 8 weeks) and 8q8/5 (Aflibercept 8 mg with 5 initial every 4 weeks followed by every 8 weeks) in participants with treatment-naïve macular oedema secondary to RVO. Data up to week 64 (end of study) were also provided in the response. The safety analysis set included all participants who had received at least one dose of study intervention (n = 892). The HD groups (i.e. 8q8/3 and 8q8/5) were pooled into the All 8 mg group. The SAF was identical to the FAS.

Exposure and Disposition

In QUASAR, 93.7% of the patient completed the study through Week 36 with more than 90% in all groups (95.0% in 2q4; 94,6% in 8q8/3 and 91.6% in 8q8/5) and more than 80% of the participants completed through Week 64 (89.4% in 2q4 arm and 88.8% in all 8 mg). The primary reasons for discontinuation were withdrawal by subject (2.6% in 2q4, 2.7% in 8q8/3 and 5.4% in 8q8/5), death (0.7% in 2q4 and 8q8/3 and 1.0% in 8q8/5) and lost to follow-up (0.7% in all arms). Similarly, through week 64, the most reported reason for discontinuation was withdrawal by subject (2.6% in 2q4 and 3.6% in all 8 mg). The mean number of active injections in the study eye was 8.5, 6.0 and 6.7 injections through week 36 and 11.2, 8.2 and 8.8 through week 64 in the 2q4, 8q8/3 and 8q8/5 treatment groups, respectively. The mean total amount of active study (mg) was 17.0, 47.6 and 53.4 mg in the 2q4, 8q8/3 and 8q8/5 treatment groups, respectively. Through Week 36, the target dosing interval of Q8 was maintained in more than 90,9% in all 8mg group and in 88,5% for 2q4. The proportions of patient who shortened to q4 dosing interval at any time was low 11.5% in 2q4, 6.6% in 8q8/3 and 9.1% in 8q8/5. Through week 64, the target dosing interval of ≥Q8 was maintained through Week 64 in 89.5% of participants in the All 8 mg group. In the All 8 mg group 4.2% vs 13% of the participants in the 2q4 group had a last completed dosing interval of Q4. In the fellow eye, the mean number of injections was 3.7, 3.4 and 4.8 in the 2q4, 8q8/3 and 8q8/5 groups, respectively.

Ocular TEAEs (study eye and fellow eye)

Ocular TEAEs in the study eye were reported in slightly higher proportion in 8q8/3 (35,5%) compared to 2q4 (28,2%) and 8q8/5 (28,9%) up to week 36. Up to week 64, ocular TEAEs in the study eye were reported in similar proportions between all 8 mg (42.6%) and 2q4 arm (42.2%). The most frequently reported ocular TEAEs in the study eye were IOP increased (5.2% in all 8 mg group vs 1.7% in 2q4 group), Visual acuity reduced (4.1% in 8q8/3, 2.7% in 8q8/5 and 1.3% in 2q8), Cataract (1.7% in 8q8/3, 3.4% in 8q8/5 and 3.0% in 2q8), Vitreous detachment (2.7% in 8q8/3, 3.0% in 8q8/5 and 0.7% in 2q8) and Conjunctival haemorrhage (3.4% in 8q8/3, 2.3 % in 8q8/5 and 2.0% in 2q8) through week 36 and IOP (2.7% in 2q4 arm and 5.9% in all 8 mg arm), Cataract (5.6% in 2q4 arm and 4.9% in all 8 mg arm) and Visual acuity reduced (4.0% in 2q4 arm and 5.5% in all 8 mg arm) through week 64.

Ocular TEAEs in the study eye were mainly mild (19.3% in 2q4 and 24.0% in all 8 mg group up to week 36) to moderate (7.0% in 2q4 and 7.1% in all 8 mg group up to week 36) in intensity. Severe ocular TEAEs in the study eye were reported in low proportions (2.0% in 2q4, 0.7% in 8q8/3 and 1.0% in 8q8/5) up to week 36. All these events occurred in single participants, apart from cataract in 2

participants in 8q8/5 group. Similarly, up to week 64, severe ocular TEAEs in the study eye remained in low proportions (2.0% in 2q4 arm and 1.0% in all 8 mg).

Up to week 36, ocular TEAEs related to the study intervention in the study eye were reported in a higher proportion in 8q8/3 (4,1%) while similar for 2q4 and 8q8/5 (2,0%). Ocular TEAEs related to study-intervention were mainly reported in single participants except for Visual acuity reduced (mild, non-serious, recovered and dose not changed in both patients in 8q8/3 group and moderate, serious, not recovered/resolved and dose interrupted and moderate, not serious, recovering/resolving and dose not changed in 2q4 arm), Macular degeneration (2 participants in 2q4 arm, the events were mild or moderate, not serious, not recovered/not resolved and drug interrupted) and IOP increased (in 9 participants in total, 0,3% in 2q4 and 1,4% in All 8 mg). Up to week 64, similarly, ocular TEAEs in the study eye assessed as related to study intervention were slightly more reported in all 8 mg arm (3.7% vs 2.0% in 2q4 arm).

Ocular TEAEs related to the injection procedure in the study eye were higher in 8q8/3 arm (13.0%) compared to 8q8/5 (8,4%) and 2q4 (6,3%). The most reported PT (≥5 participants in total) were Conjunctival haemorrhage (1,7% in 2q4 and 2,4% in All 8 mg), IOP increased (1.0% in 2q4 and 2.5% in All 8 mg) and Eye pain (0,7% in 2q4 and 0,8% in All 8 mg).

Ocular TEAEs related to protocol-required procedure in the study eye were low and slightly higher in all 8 mg (1,9% vs 1,0% in 2q4) and occurred in single participants except IOP increased (4 participants in all 8 mg group) and Conjunctival haemorrhage (one participants in each group).

The most reported ocular TEAEs in the fellow eye were Cataract (1,9% in all 8 mg group and 3,0% in 2q4 group). Incidences of ocular TEAEs in the fellow eye were well balanced across treatment groups. No TEAEs were assessed as related to aflibercept 2 mg in the fellow eye. One TEAE assessed as related to injection procedure occurred in the fellow eye in the 8q8/3 group.

Non-ocular TEAEs

Non-ocular TEAEs were reported in slightly lower proportions in 8q8/3 arm (47,1%) while being comparable between All 8 mg group (49,1%) and 2q4 (50,2%) up to week 36. Up to week 64, non-ocular TEAEs occurred in similar proportions in both arms (62.8% in 2q4 and 62.3% in all 8 mg). For non-ocular TEAEs, the most reported SOC were Vascular disorders (5,3% in 2q4 and 8,3% in all 8 mg) and Infections and Infestations (19,3% in 2q4 and 18,8% in all 8 mg) with the PT Hypertension (3,3 % in 2q4, 6,5% in 8q8/3 and 6,7% in 8q8/5) and Nasopharyngitis (3,0 % in 2q4, 5,1% in 8q8/3 and 4,7% in 8q8/5) which were consistent with the study population and observed imbalances in incidence of reported non-ocular medical history between treatment arms (61.9% in the All 8mg group compared to 57.5% in the 2q4 group for Hypertension). Up to week 64, the most reported non-ocular TEAEs were Nasopharyngitis (6.6% in 2q4 arm and 8.8% in all 8 mg) and Hypertension (5.0% in 2q4 arm and 10.6% in all 8 mg group), however all events were non-serious, mostly mild or moderate and not assessed as related to study intervention.

Up to week 36, non-ocular TEAEs were mild (27,9% in 2q4 and 30,6% in All 8 mg) to moderate (16.9% in 2q4 and 15,1 % in All 8 mg) in intensity. Severe non-ocular TEAEs were reported mainly in single participants except for Bradycardia and Sepsis (2 participants each in 8q8/3) and type 2 diabetes mellitus (2 participants in the 2q4 group). Up to week 64, severe non-ocular TEAEs occurred in low proportions in both treatment groups (7.3% in 2q4 arm and 6.4% in all 8 mg).

Non-ocular TEAEs assessed as related to study intervention were low (0.3% in 2q4 and 0.5% in all 8 mg). Non-ocular TEAEs related to study intervention were reported in two participants in 8q8/3 Atrioventricular block first degree (mild, dose not changed, PR interval increased not significant with new ECG normal) and Headache (also assessed as related to protocol required procedure, moderate, dose

not changed and recovered/resolved), 1 participant in 2q4 Haemoglobin increased (severe, drug interrupted, non-serious, recovered/resolved) and 1 participant in 8q8/5 Rash (mild, drug interrupted, non-serious, recovered/resolved). Non-ocular TEAEs related to injection procedure occurred in one patient in 2q4 who presented multiple events of non-serious mild headache (all recovered and dose not changed). Non-ocular TEAE related to protocol required procedure were reported in comparable proportions (1.0% in 2q4 and 1.5% in all 8 mg group) and occurred in single participants except for Nausea. Up to week 64, non-ocular intervention-related TEAE were observed in low and comparable proportions 0.7% in 2q4 arm and 0.8% in all 8 mg group.

Deaths

Through week 36, 7 deaths occurred in comparable proportions between treatment arms (0,7% in 2q4 and 8q8/3 and 1,0% in 8q8/5 group). None of the deaths were assessed as related to study intervention or study procedure. Deaths were reported in 3 additional patients in 2q4 arm (1.0%) and 7 patients in all 8 mg arm (1.2%) up to week 64.

Ocular and non-ocular TEAEs leading to study intervention discontinuation

Ocular TEAEs in the study eye leading to study intervention discontinuation were low 0.3% in 2q4 and 0.2% in All 8 mg group and consisted of Macular hole in 2q4 group (severe, serious, not recovered/not resolved, related to injection procedure) and Retinal vasculitis in 8q8/5 group (moderate, serious, not recovered/not resolved, related to study intervention). Non-ocular TEAEs leading to study intervention discontinuation were low, comparable (1.0% in 2q4 and 0.8% in all 8 mg group) and reported in single participants.

Up to week 64, Incidence of ocular TEAEs leading to study discontinuation were low in both groups (0.3%). Non-ocular TEAEs leading to study discontinuation remained in low and comparable proportions 1,3% in 2q4 arm, 1,0% in 8q8/3 and 1.3% in 8q8/5 arms.

Serious ocular and non-ocular TEAEs

Serious ocular TEAEs in the study eye were low and higher in 2q4 (2.3% vs 1.2% in all 8 mg group) up to week 36. Similarly, up to week 64, ocular TESAE in the study eye occurred in low proportions, 2.7% participants in 2q4 arm and 1.7% in all 8 mg group.

All events up to week 36 were reported in single participants across treatment groups except Endophthalmitis (2 participants in 2q4 and 1 in 8q8/3 groups), Visual acuity reduced (1 participant in 8q8/5 and 2q4 groups) and Macular hole (2 participants in 2q4). Similarly, up to week 64, Endophthalmitis was reported in 3 participants in the 2q/4 group and 1 in the 8q8/3 group, Macular hole was reported in 2 participants in the 2q4 group, and Visual acuity reduced was reported in 1 participant each in the 8q8/5 group and the 2q/4 group. Ocular SAE in the study eye were mostly moderate (1,3% in 2q4 and 0,7% in All 8 mg) to severe (1,0% in 2q4 and 0,3% in All 8 m). Up to week 64, the maximum intensity of these SAEs was mostly moderate (5 [0.8%] participants in the All 8mg group and 4 [1.3%] participants in the 2q4 group) or severe (4 [0.7%] in the All 8mg group and 4 [1.3%] participants in the 2q4 group). Serious ocular TEAEs in the study eye related to study intervention (0,7% in 2q4 and 0,3% in 8q8/5) and injection-procedure (1,3% in 2q4 and 0,3% in 8q8/3 and 8q8/5) were low. Six events were assessed as related to IVT injection procedure (Endophthalmitis in 2 participants in the 2q4 group and 1 participant in the 8q8/3 group, Macular hole and Retinal detachment each in 1 participant in the 2q4 group, and Cataract in 1 participant in the 8q8/5 group) and three events to study intervention (Retinal vasculitis in 1 participant in the 8q8/5 group, and Visual acuity reduced and Endophthalmitis each in 1 participant in the 2q4 group). The outcomes for all events of Endophthalmitis and the event of Cataract were recovered/resolved or recovered/resolved with sequela. The outcome for the event of Retinal detachment was recovering/resolving. The outcomes for the events of Macular hole and Visual

acuity reduced were not recovered/not resolved at the time of the week 36 data cut. Up to week 64, serious ocular TEAEs were assessed as related to IVT injection for seven events (Endophthalmitis in 3 participants in the 2q4 group and 1 participant in the 8q8/3 group, Macular hole and Retinal detachment each in 1 participant in the 2q4 group, and Cataract in 1 participant in the 8q8/5 group) and assessed as related to study intervention in three events (Retinal vasculitis in 1 participant in the 8q8/5 group, and Visual acuity reduced and Endophthalmitis each in 1 participant in the 2q4 group). The maximum intensity was moderate (5 [0.8%] participants in the All 8mg group and 4 [1.3%] participants in the 2q4 group) or severe (4 [0.7%] in the All 8mg group and 4 [1.3%] participants in the 2q4 group). Seven events were assessed as related to IVT injection and three assessed as related to study intervention. Events were recovered/resolved for 4 events, recovered with sequelae for 3 events and not recovered/not resolved for two events.

Ocular serious TEAEs in the fellow eye were reported in one participants in the 8q8/3 group (Choroidal detachment, Glaucoma and Flat anterior chamber of eye, all severe and resolved or resolving). None were assessed as related to study intervention or IVT injection procedure.

Serious non-ocular TEAEs were comparable between treatment arms (8,3% in 2q4, 7,2% in 8q8/3 and 7,4% in 8q8/5 groups). Non-ocular SAEs were mainly severe (3,6% in All 8 mg and 4,7% in 2q4 group) to moderate (2,9% in All 8 mg and 3,3% in 2q4 group). The most frequent non-ocular serious TEAEs was Pneumonia, which was reported in 1 (0.3%) participant in the 8q8/3 group and 2 (0.7%) participants in the 2q4 group. None of the non-ocular serious TEAEs was assessed to be related to study intervention or IVT injection procedure. Up to week 64, non-ocular TESAEs were reported in similar proportions, 12.0% in 2q4 arm and 11.2% in all 8 mg arm.

Adverse events of interest

AESI were reported in higher proportions in 2q4 group (3,0% vs 1,0% in all 8 mg group) and mainly in single participants except for Coronary artery disease (1 participant each in the 8q8/3 and 2q4 groups) and Cerebral infarction (1 participant each in the 8q8/5 and 2q4 groups). No events of Retinal pigment epithelial tear in the study eye were observed.

Intraocular Inflammation

TEAEs of intraocular inflammation in the study eye occurred in slightly higher proportion in 2q4 (1,3% compared to 0,3% in 8q8/5 and 0,7% in 8q8/3). All events were reported in single participants except Endophthalmitis and were mainly moderate or mild and recovered/resolved. In 2q4 group, both cases of Endophthalmitis were moderate, serious, related to injection procedure (one was also related to study intervention), recovered/resolved with sequelae for one and dose interrupted for one. In 8q8/3 group, the case of Endophthalmitis was severe, serious, related to injection procedure and recovered/resolved with sequelae with dose not changed. The case of Eye inflammation in 2q4 was moderate, non-serious, related to study intervention, recovered/resolved with dose not changed. The case of Anterior chamber cell in 2q4 was non-serious, mild, recovered/resolved and not related. The event of Uveitis in 8q8/5 group occurred twice in one participant, both events were non-serious, moderate, recovered/resolved and assessed as not related. The event of Iritis in 8q8/3 was non-serious, mild, recovered/resolved and assessed as not related. Similar tendencies were observed up to week 64 (1,7% in 2q4 arm vs 1,0 % in all 8 mg group).

Cataract

Cataract was a frequent medical history reported in comparable proportions (48.9% of participants in the All 8mg group and 49.2% of participants in the 2q4 group). Events of Cataract were reported in similar proportions between all 8 mg group (3,3% in 2q4 group and 3,4% in all 8 mg). Events of Cataract

were mainly mild (1,3% in 2q4 group and 2,9% in all 8 mg group) and not recovered/ not resolved (1,3% in 2q4 group and 3,0% in all 8 mg group) through Week 36.

IOP increase

TEAEs of IOP increased in the study eye were reported in higher proportions in all 8 mg (6,3% vs 3,0% in 2q4 group). None of the events were serious or lead to study intervention discontinuation. Most of the events were mild (3,0% in 2q4 group and 4,4% in all 8 mg group) and recovered/resolved (1,7% in 2q4 group and 3,7% in all 8 mg group). There was a slightly higher proportion of participants in the All 8 mg group than the 2q4 group for all criteria except for the clinically most relevant IOP assessment of ≥ 35 mm Hg (pre- or post-dose). Proportions of participants with Paracentesis in the study eye by Week 36 was low and similar across the treatment groups.

Up to week 64, proportions of patients with IOP assessment of ≥35 mmHg (pre- or post-dose) was well balanced between the All 8mg group (1.2%) and the 2q4 group (0.7%).

Retinal tear/retinal detachment

Retinal tear detachment or Retinal tear were reported in 4 participants; Retinal tear in 1 (0.3%) participant in the 8q8/3 group and 2 (0.7%) participants in the 8q8/5 group, and Retinal detachment in 1 (0.3%) participant in the 2q4 group. The event of Retinal detachment was serious, severe, related to the injection procedure and resolving. Events of Retinal tear were mild, non-serious, recovered/resolved or not recovered/not resolved and one event was assessed as related to injection procedure (in 8q8/3 group).

APTC events and ATE

APTC events were reported in 5 participants in 2q4 group and 3 participants in 8q8/5 group. All events were reported in single participant except for Myocardial infarction (1 participant each in the 8q8/5 group and the 2q4 group). Events were mainly mild to moderate in intensity and recovered/resolved. Two cases had a fatal outcome (Haemorrhage intracranial and Brain herniation). None were assessed as related to study intervention or injection procedure.

Up to week 64, APTC events occurred in 8q8/3 group (2 [0.7%] participants),8q8/5 group (8 [2.7%]) and 2q4 group (9 [3.0%]) and in single participants except Coronary artery disease (1 participant in each of the 2q4, 8q8/3 and 8q8/5 groups), Myocardial infarction (1 participant in each of the 8q8/3 and 8q8/5 groups) and Acute myocardial infarction and Cerebral infarction (each in 1 participant in the 8q8/5 and 2q4 groups, respectively).

TEAEs of ATE were reported in low proportions 3,7% in 2q4 group and 2,2% in all 8 mg arm (2,7% in 8q8/5 and 1,7% in 8q8/3). Events reported in more than 2 participants across treatment arms were Blood creatine phosphokinase increased, Coronary artery disease, Cerebral infarction, and Carotid arteriosclerosis. ATE events were mostly mild in intensity and recovering/resolving or not recovered/not resolved through week 36. TESAE were reported for 4 participants in 2q4 group and 2 participants in all 8 mg group. None of the ATE events was assessed to be related to the study intervention or injection procedure.

Hypertension

Medical history of Hypertension was reported in higher incidence in the all 8 mg group (61,9% vs 57,5% in 2q4 group). Events related to Hypertension were reported in higher proportion in the all 8 mg group (8,1% vs 4,7%). These events were mainly mild (3,3% in 2q4 group and 5,9% in all 8 mg) in intensity and severe in one participants in 2q4 group and 8q8/3 group The reported outcomes were recovered/resolved (2,4% in all 8 mg group vs 1,0% in 2q4 group), recovering/resolving (2,0% in all 8 mg group vs 2,3% in 2q4 group) and not recovered/not resolved (3,6% in all 8 mg group vs 1,3% in

2q4 group) through week 36. TESAE of hypertension were reported in one participants in 2q4 group (severe in intensity, not related to study intervention, not related to protocol-required procedures, not related to intravitreal injection).

Up to week 64, similar tendencies are observed (all 8mg group (11.3%) vs 2q4 group (7.0%)) which is consistent with the imbalance in incidence of medical history of Hypertension with 65.7% in the All 8mg group compared to 62.1% in the 2q4 group.

There was no increase from baseline in mean SBP and DBP through Week 36 and 64. The proportion of participants with pre-defined treatment-emergent potentially clinically significant values (PCSVs) for SBP or DBP was low, and no notable differences were observed across the treatment groups.

Nasal mucosal findings

Nasal mucosal events consisted of Epistaxis reported in 2 participants each in the 8q8/3 and 2q4 groups (0,7%) and 1 (0.3%) participant in the 8q8/5 group. None were assessed as related to study intervention or injection procedure, all were resolved and one event was moderate and serious in the 2q4 group.

Non-ocular haemorrhage

TEAEs of non-ocular haemorrhage were reported in 3,2% in All 8 mg group and 2,0% in 2q4 group. These events were mainly mild in intensity (1,3% in 2q4 and 2,0% in All 8 mg), non-serious and recovered/resolved (1,0% in 2q4 group and 1,9% in all 8 mg). Serious TEAEs of non-ocular haemorrhages were reported in 7 participants in comparable proportions across treatment groups (0.8% in the All 8mg group and 0.7% in the 2q4 group). None were assessed as related to study intervention or injection procedure. Two events lead to study intervention discontinuation: Haemorrhage intracranial (with fatal outcome) in 2q4 group and Subdural haematoma in 8q8/5 group.

VTE events

Incidences of VTE events were comparable across treatment groups (1.3% in 2q4 group and 1.9% in all 8 mg group). All events were mild and moderate non-serious except for an event of mild Retinal vein occlusion in 8q8/5 group which was resolved and not related to study intervention or injection procedure.

Hypersensitivity

TEAEs of hypersensitivity were reported in low proportions 0.7% in 2q4 group and 1.5% in all 8 mg group. All events were mild or moderate and were mainly recovered/resolved. One TESAE occurred of moderate event of Anaphylactic reaction in 8q8/3 group which was assessed as not related to study intervention and resolved. One recovered mild non-serious event of rash was assessed as related to study intervention.

ADRs

Based on the 36 and 64 Weeks data, no new ADRs are proposed for inclusion. There was no meaningful difference in the incidence and nature of events reported across the All 8mg and 2q4 treatment groups. Changes were made in section 4.8 of the SmPC (frequencies, ADR shifted from expected to observed with 114.3 mg/mL) which are endorsed.

Extrinsic and Intrinsic factors

Subgroup analysis showed no clinically relevant differences among treatment group. Few participants received bilateral treatment (1.7% in all 8 mg group and 3.0% in 2q4 group). No clinically meaningful differences could be observed across treatment groups.

Post-marketing data

No new signal was identified from post-marketing data. The next PSUSA for Aflibercept PSUSA/00010020/202511 is expected for mid-2026.

Q4 dosing: safety analysis

Currently Eylea 8 mg is indicated in DME and nAMD at the posology of 1 injection per month for 3 consecutive doses then injection intervals may then be extended up to every 4 months (Q16) followed by every 5 months (Q20) such as with a treat-and-extend dosing regimen, while maintaining stable visual and/or anatomic outcomes. The shortest interval between 2 injections is 2 months (Q8) in the maintenance phase and the Applicant submitted this variation to provide safety data in support of shortening to Q4 interval during the maintenance phase. This modification is proposed to align with the proposed posology of RVO which is 1 injection per month for 3 consecutive doses than injection intervals may then be extended based on the physician's judgement of visual and/or anatomic outcomes. The interval between 2 injections should not be shorter than 1 month.

The safety analysis consists of safety data from day 1 to Week 12 of the initiation phase for PULSAR, PHOTON and QUASAR in 2mg arm and HD groups. The Applicant provided discussion on the ocular and non-ocular TEAEs by SOC and PT, relatedness, seriousness and intensity, including safety topics, for which occurred from day 1 through Week 12 (before the 4th injection) for all three studies.

Overall, in PULSAR 672 participants with nAMD received a total of 2,001 HD aflibercept injections at Q4 intervals with a mean of 3 injections per participant. In PHOTON, 491 participants with DME received a total of 1,455 HD aflibercept injections at Q4 intervals with a mean of 3 injections per participant from day 1 though Week 12. For QUASAR, through Week 36, a total of 591 participants received a total of 2,470 HD aflibercept injections at Q4 intervals in QUASAR.

PULSAR (nAMD)

In PULSAR, ocular TEAEs occurred in comparable proportions between all HD group (18.1%) and 2q8 (17.3%). Events reported in more than 2 participants during the initiation phase in the all HD group and with a $\geq$ 0.5% difference to 2q8 in both the HD12 and HDq16 arms were retinal haemorrhage (2q8: 0.9%, all HD: 1.8 % in the study eye and 0% 2q8 and 0,6% in all HD), conjunctivitis (2q8: 0%, all HD: 0.7%), IOP increase (2q8: 0,9%, all HD: 1,5%), and vitreous floaters (2q8: 1.8%, all HD: 1.9%). These events are either listed in the SmPC of Eylea or common ocular condition.

Ocular study drug related TEAEs occurring during the initial monthly dosing phase were reported in higher proportion in all HD group (2,2% vs 0,9% in 2q8). Study drug related ocular TEAEs were all observed in less than 1% of the subjects and reported mostly in single participants except retinal haemorrhage and retinal pigment epithelial tear which are known common AEs of Aflibercept. Ocular serious TEAEs were reported in similar proportions (0.3% 2q8, one case of retinal haemorrhage vs 0.3% All HD, 2 events in HDq16, retinal haemorrhage and angle closure glaucoma). Ocular TEAEs were mostly mild (14.3% vs 13.7%, 2q8 vs All HD) to moderate (2.7% vs 4.3%, 2q8 vs All HD) in intensity and severe Ocular TEAEs were retinal haemorrhage reported once in 2q8 and HDq16

Regarding ocular safety topics through week 12, comparable frequencies were observed for cataract (0,6% in 2q8 and 0,9% in all HD) and retinal pigment epithelial tear (0,9% in 2q8 and 1,3% in all HD). For IOP increase (2q8: 0,9%, all HD: 1,5%), all events occurring were all non-serious and without sustained IOP elevations. As 8 mg aflibercept is injected within 70 µl and the 2 mg dose within 50 µl, higher frequency of IOP increase may be expected however study pre-injection IOP measurements remained stable during the initiation phase.

The incidence rates for safety topics assessed as study drug related were low and similar between patients treated with 2 mg and those treated with 8 mg treated. Serious events were low (less than 1%) and similar in range. Events were mostly mild to moderate and severe events were low and similar between 2 mg and 8 mg treated patients.

Non-ocular TEAEs were reported in higher proportion in the HD arms (22.1%) than in 2q8 arm (16.7%). The SOC "Infection and Infestations" and "Vascular disorders" were more reported in the HD arms with a difference of > 1% compared to 2q8, respectively 4.9% vs 3.3% and 2.5% vs 1.2%. For both SOCs, majority of the PT were reported in single participants except Pulpitis dental, Upper respiratory tract infection, Urinary tract infection which may be expected in the elderly population. For the SOC "Vascular disorders", the most reported PT was Hypertension which was reported in similar proportions through Week 12 (1,8% in 2q8 and 2,5% in HD arms). Non-ocular study drug related TEAEs occurring during the initial monthly dosing phase were cerebrovascular accident (2q8) and pulmonary embolism (HDq16). Serious non-ocular TEAEs were reported mostly in single participants and in total in 8 participants [2.4%] in the HDq12 group, 12 participants [3.6%] in the HDq16 group and 14 participants [4.2%] in the 2q8 group. Furthermore, the majority of the events were mild and no severe events were reported in the all HD group. The majority of the patient recovered or recovering and comparable proportions of patient not recovered were reported in both 2q8 and all HD group (1.5% vs 1.8%).

Regarding systemic safety topics, the incidence between 2 mg and 8 mg treated patients were low and comparable (Hypersensitivity 0,6% in HD arms and 0,3% in 2q8 arm; Hypertension 2,5% in HD arms and 1,8% in 2q8 arm; Non ocular haemorrhage 0,3% in both HD and 2q8 arms; Cardiovascular ischemic events 0,3% in both HD and 2q8 arms; Cerebrovascular ischemic events 0,6% in both HD and 2q8 arms; VTE 0,1% in HD arms and 0% in 2q8 arms; ATEs 0,9% in both HD and 2q8 arms; APTCs events 0,1% in HD arms and 0,9% in 2q8 arm; Nasal mucosal events 0,1% in HD arms and 0% in 2q8 arm).

PHOTON (DME)

Ocular TEAEs in the initiation phase were higher in HD groups compared to 2q8 (17,1% vs 9,6%) however this difference may be driven by a lower rate in the 2q8 arm in PHOTON during the treatment initiation than in PULSAR (PULSAR - 2q8: 17.3%, PHOTON – 2q8: 9.6%). Furthermore, ocular TEAEs in the fellow eye also showed a higher incidence in the HD arms versus 2q8. Events were reported in single participants and difference higher than 0,5% were seen for cataract (0,8% in HD arms vs 0% in 2q8)/cataract cortical (0,6% in HD arms vs 0% in 2q8), conjunctival haemorrhage (3,1% in HD arms vs 1,2% in 2q8), photopsia (0,6% in HD arms vs 0% in 2q8), punctate keratitis (1,2% in HD arms vs 0,6% in 2q8), and vitreous detachment (1,4% in HD arm vs 0% in 2q8). All these events are known ADR or Eylea which are either known as injection related (Vitreous detachment, cataract/cataract cortical and Conjunctival haemorrhage) or also seen in higher proportion in the fellow eye (photopsia and punctuate keratitis).

Study drug related ocular TEAEs occurring during the initial monthly dosing phase were reported mostly in single participants except intraocular pressure increased and in low proportions (0,6% in 2q8 and 1,2% in all HD group). Serious ocular TEAEs occurred in single participant and were reported in similar proportions (0,6% in 2q8 and 0,4% in all HD group). None were considered related to the study drug. Ocular TEAEs were mild (9.0% vs 15.1%, 2q8 vs All HD) to moderate (0.6% vs 1.4%, 2q8 vs All HD) and severe Ocular TEAEs were reported in low proportions (0% vs 0.6%, 2q8 vs All HD), and in single patients. None were considered related to the study drug.

Ocular safety topics, except for cataract, were reported in comparable proportions between treatment arms (IOP increase 1,4% in HD arms and 1,2% in 2q8 arm; IOI 0,6% in HD arms and 0,6% in 2q8 arm and retinal tear/retinal detachment 0,2% in HD arms and 0% in 2q8). The incidence rates for safety topics assessed as study drug related were low (less than 1%) and were reported in single participants except for IOP increased and IOI. The incidences of serious events between 2 mg and 8 mg treated patients were low and similar in range. Events were mainly mild to moderate and incidence of severe TEAEs were low and comparable between patients treated with 2 mg and 8 mg doses.

For non-ocular TEAEs in PHOTON through Week 12, SOC with a difference of > 1% and higher in the HD arms were Gastrointestinal disorders 2.4% in HD arms and 1.2% in 2q8 arm), Infections and infestations (8.2% in HD arms and 4.2% in 2q8 arm), Nervous system disorders (3,5% in HD arms and 1,8% in 2q8 arm), Psychiatric disorders (1.4% in HD arms and 0% in 2q8 arm), Renal and urinary disorders (2.2% in HD arms and 0.6% in 2q8 arm) and Respiratory, thoracic and mediastinal disorders (1.2% in HD arms and 0% in 2q8 arm). In these SOCs, events were reported mostly in single participants or were common conditions in the DME population and/or not considered related to an intravitreal anti-VEGF effect.

Non-ocular study drug related TEAEs during the initial monthly dosing phase occurred in only one patient (lacunar infarction, mild in intensity, non-serious, patient with underlying risk factors (e.g. diabetes mellitus)). Non-ocular serious TEAEs were more reported in all HD group (3.6% vs 6.3%, 2q8 vs All HD group) but no differences above 1% were seen between SOC. Non-ocular serious TEAEs reported in ≥2 participants in any treatment group were Myocardial infarction (3 [0.6%] patients), COVID-19 (3 [0.6%] patients) and Acute kidney injury (3 [0.6%] patients). None were considered as related to study drug. Non-ocular TEAEs were mainly mild (14.4% vs 13.0%, 2q8 vs All HD) to moderate (6.0% vs 7.1%, 2q8 vs All HD) and severe non-ocular TEAEs were reported in 5 participant [3.0%] vs 21 participants [4.3%], 2q8 vs All HD) and mostly observed in single participants except for myocardial infarction, COVID-19 and acute kidney injury. None were considered related to the study drug.

Non-ocular safety topics were reported in similar or comparable proportions (Hypersensitivity 0.6% in both HD and 2q8 arm; Hypertension 4.1% in HD arms and 5.4% in 2q8 arm; Non-ocular haemorrhage 0.6% in both HD and 2q8 arms; Cardiovascular ischemic events 1.0% in HD arms and 1.8% in 2q8 arm; Cerebrovascular ischemic events 0.4% in HD arms and 0% in 2q8 arms; ATEs 1.2% in HD arms and 1.8% in 2q8 arms; APTCs events 1.0% in HD arms and 0.6% in 2q8 arm; Nasal mucosal events 0% in both HD and 2q8 arms).

QUASAR (RVO)

In QUASAR, incidence of ocular TEAEs was slightly higher in HD arms (16.6% vs 13.6% in 2q4 arm). Ocular TEAEs reported through Week 12 in more than 2 participants and with a difference >0.5% were vitreous detachment (0% in 2q4 arm and 0,7% in HD arms) and intraocular pressure increased (1.3% in 2q4 arm and 3.6% in HD arms) which are known ADR of Eylea. All events of IOP increased during the loading phase of QUASAR were non-serious and pre-injection IOP measurements remained stable without indication for sustained IOP elevations.

Study drug related ocular TEAE occurring during the initial monthly dosing were reported in low proportions and in single participants except visual acuity reduced (0.7% vs 0.3%, 2q4 vs All 8mg) and intraocular pressure increased (0% vs 1.2%, 2q4 vs All 8mg). A low proportion of patients experienced a serious ocular TEAE (1.3% vs 0.3%, 2q4 vs All 8mg. Ocular TEAEs were mild (9.3% vs 13.5%m, 2q4 vs All 8mg) to moderate (3.3% vs 2.9%, 2q4 vs All 8mg) in intensity and severe events were reported in single participants in 3 (1.0%) patients in the 2q4 group and 1 (0.2%) patient in the All 8mg group.

For ocular safety topics (cataract, IOI and retinal tear/detachment), no differences were seen except for IOP increased. Events related to safety topics assessed as study drug related were intraocular pressure increased and hypersensitivity. The incidence of serious TEAEs among patients treated with 2 mg and 8 mg doses was low and similar in range or occurred only in single participants. Events were mostly mild to moderate and severe events were observed in low proportions and in a comparable range between 2 mg and 8 mg treated patients.

In QUASAR, non-ocular TEAEs were reported in lower incidences in the HD groups compared to 2q4 (22,8% vs 26,6%). The SOC Vascular Disorders was more reported in the HD arms (4,6% vs 3,0% in 2q4 arm). All events were reported in single participants except Hypertension (4,7% in HD arms vs 3,3% in 2q4 arm) which may be explained by the imbalance in medical history (61.9% in All 8mg group and

57.5% in the 2q4 group). No increase from baseline in mean systolic blood pressure and diastolic blood pressure was observed through Week 36. Other systemic safety concern (Hypersensitivity, Non-ocular haemorrhage, VTE, ATE, APTC events and Nasal mucosal events) were either comparable between treatment arms or reported in higher incidence in 2q4 arm. Non-ocular TEAEs occurring during the initial monthly dosing phase were related to study drug in only two patients (rash, non-serious, mild intensity recovered with remedial treatment in the 8q8/5 group and headache, non-serious, moderate intensity, related to study drug and protocol required procedure, recovered without remedial treatment in the 8q8/3 group). Serious non-ocular TEAEs were reported in single participants in 11 participants (1.9%) in the All 8mg group and 9 participants (3.0%) in the 2q4 group. Non-ocular TEAEs were mild (16.9% vs 16.4%, 2q4 vs All 8mg) to moderate (8.6% vs 5.1%, 2q4 vs All 8mg) in intensity and severe TEAEs were reported in single participants in similar proportions 1.0% vs 1.4%, 2q4 vs All 8mg.

In all three studies, no safety concern is raised, reported ocular TEAEs in the study eye during the initiation phase are in line with the safety profile of Eylea and no issue is raised regarding non-ocular TEAEs.

2.5.2. Conclusions on clinical safety

The safety profile of Eylea HD in RVO (CRVO/BRVO) at the proposed posology of 1 injection per month for 3 consecutive doses followed by a treat-and-extend showed to be consistent with the known safety profile of HD Eylea and with the 2 mg posology. Moreover, provided safety data of the initiation phase for all three studies (PULSAR, PHOTON and QUASAR) are in support of shortening to Q4 interval during the maintenance phase.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 36.1 is acceptable.

Safety concerns

Table 143: Summary of safety concerns

Important identified risks	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Cataract (especially of traumatic origin)
Important potential risks	• Medication errors • Off-label use and misuse • Embryo-fetotoxicity
Missing information	• Long-term safety of aflibercept in preterm infants with ROP • Exposure with bilateral 8 mg aflibercept therapy

Pharmacovigilance plan

Table 144: On-going and planned additional PV activities

Study Status	Objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional Pharmacovigilance (PhV) activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).				
Review safety outcomes of FIREFLEYE NEXT study BAY 86-5321/20275: An extension study to evaluate the long-term outcomes of subjects who received treatment for retinopathy of prematurity in Study 20090 Status: Ongoing	• Primary study objective: To evaluate long-term safety outcomes and visual function of subjects included in Study 20090 for treatment for retinopathy of prematurity (ROP) • Secondary study objective: To describe the visual function and overall development of subjects included in Study 20090 for treatment for ROP	• The purpose of the current study is to collect the missing data of the potential long-term effects after treatment with aflibercept and laser. Subjects will be followed up to 5 years of chronological age, which will enable a detailed assessment of visual function and overall development.	Protocol finalized (27 NOV 2019) LPLV: planned for OCT 2025	Interim study report: • 2-year of age data in Q2 2023 • 3-year of age data in 2024, • 4-year of age data in 2025 Final study report 2026

Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).

Risk minimisation measures

Table 145: Summary table of pharmacovigilance activities and risk minimization activities by safety concern for Eylea 40 mg/mL (0.4/2 mg doses) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet (for adults and babies born prematurely) section 2, 3, and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for any post-marketing or study reports suspicious

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (adult indications) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications: patient guide "Your guide to Eylea", and its audio version).	for endophthalmitis and intraocular inflammation (see **Annex 4.1**). **Additional pharmacovigilance activities:** None
Intraocular inflammation	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet (for adults and babies born prematurely) section 2, 3, and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (adult indications) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications: patient guide "Your guide to Eylea", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see **Annex 4.1**). **Additional pharmacovigilance activities:** None
Transient intraocular pressure increase	**Routine risk minimization measures:** SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet (for adults and babies born prematurely) sections 2 and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
		Specific questionnaire to be used for any post-marketing or study report regarding IOP increase following the use of the Bayer Eylea pre-filled syringe.
	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections	
	Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (adult indications) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications: patient guide "Your guide to Eylea", and its audio version).	**Additional pharmacovigilance activities:** None
Retinal pigment epithelial tears	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 Package Leaflet sections 2 and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable.
	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections	**Additional pharmacovigilance activities:** None
	Additional risk minimization measures: Educational program for adults: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video, patient guide "Your guide to Eylea", and its audio version).	
Cataract (especially of traumatic origin)	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 Package Leaflet sections 2, 3, and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (adult indications) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications: patient guide "Your guide to Eylea", and its audio version).	**Additional pharmacovigilance activities:** None
Medication errors	**Routine risk minimization measures:** SmPC sections 4.2, 4.9, and 6.6 Package Leaflet sections 1 and 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections. Packing differentiation Eylea 40 mg/ml versus Eylea 114.3 mg/ml. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video; in addition, for adult indications: patient guide "Your guide to Eylea", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Off-label use and misuse	**Routine risk minimization measures:** SmPC sections 4.1, 4.3, 4.4, and 4.6 Package Leaflet sections 1, 2, and 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' (adult indications) and physicians' awareness on off-label use (prescriber guide and video; in addition, for adult indications: patient guide "Your guide to Eylea", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None
Embryo-fetotoxicity	**Routine risk minimization measures:** SmPC sections 4.4, 4.6, and 5.3 Package Leaflet section 2 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program for adults: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	and video, patient guide "Your guide to Eylea", and its audio version).	
Long-term safety of aflibercept in preterm infants within ROP	**Routine risk minimization measures:** SmPC section 4.4 and 4.8 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** FIREFLEYE NEXT Phase IIIb study
Exposure with bilateral 8 mg aflibercept therapy	**Routine risk minimization measures:** SmPC section 4.4/5.1	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** The safety associated with 8 mg aflibercept bilateral administration will be monitored in the PSUR. **Additional pharmacovigilance activities:** Not applicable.

2.7. Update of the Product information

As a consequence of this new indication and an updated posology, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: The content of the proposed package leaflet is largely identical to the Eylea 114.3 mg/ml tested in the line extension procedure EMEA/H/C/002392/X/0084/G.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Retinal Vein Occlusion (RVO) is among the most common causes of vision loss resulting from diseases that affect the retinal blood vessels. There are two primary types of RVO:

- Central Retinal Vein Occlusion (CRVO), which involves a blockage of the central vein responsible for draining blood from the retina, and
- Branch Retinal Vein Occlusion (BRVO), where one or more branches of the central retinal vein are obstructed.

A less common subtype, Hemi-Retinal Vein Occlusion (HRVO), occurs when branches in either the superior or inferior hemisphere of the retina are blocked, sharing features of both CRVO and BRVO.

All RVO subtypes impair venous outflow from the eye, potentially leading to increased venous pressure, decreased arterial perfusion, and retinal ischemia. One of the consequences of retinal non-perfusion is elevated production of Vascular Endothelial Growth Factor (VEGF). In fact, VEGF levels in the aqueous humor of eyes with RVO can exceed normal levels by more than 100-fold.

This overexpression of VEGF promotes vascular permeability, macular edema, retinal hemorrhages, and neovascularization. As a result, patients with macular edema secondary to RVO experience loss of visual acuity, and without treatment, the visual prognosis is generally poor.

3.1.2. Available therapies and unmet medical need

Although anti-VEGF therapy is the standard-of-care for nAMD, DME and RVO, the patients', physicians', and caregivers' burden remain considerable with regard to the number of intravitreous (IVT) injections, in particular during long-term treatment.

Therefore, the Applicant has developed a novel formulation (aflibercept 8 mg) for IVT injections, which has the potential to decrease the number of IVT injections and at the same time increase intervals between patients' visits for the treatment of nAMD and DME.

3.1.3. Main clinical studies

The clinical development program of aflibercept (8 mg dose) for the new RVO indication consisted of one - pivotal study QUASAR (22153); an ongoing (with data through Week 64), multicenter, randomized, double-masked, active-controlled Phase 3 study in participants with RVO.

In addition to support the Q4 dosing interval option for nAMD, and DME data from four studies QUASAR (22153), PULSAR (20968), PHOTON (21091), CANDELA (21086) have been analysed.

3.2. Favourable effects

QUASAR study: RVO indication

The efficacy profile of Aflibercept 8 mg (114.3 mg/ml) up to Week 36 for the RVO (CRVO/BRVO/HRVO) indication in adults is comparable to the established efficacy profile of Eylea of either formulation.

For the QUASAR study, data provided by the Applicant through Weeks 36 and 64 show that the **primary endpoint** - BCVA change from baseline at Week 36 - was met at Week 36 for the 8q8/3 and 8q8/5 treatment arms.

For both arms, 8q8/3 and 8q8/5, non-inferiority to Eylea 2q4 on the BCVA change from baseline at Week 36 was demonstrated within the prespecified margin of 4 letters ($p<0.001$, at a one-sided significance level of 0.025).

Regarding these results the primary endpoint is achieved in the pooled RVO group in terms of BCVA improvements at Week 36.

Concerning the **key secondary endpoint** - number of active injections from baseline to week 64 - according to the results provided by the Applicant, the 8q8/5 and 8q8/3 groups received a statistically significantly lower number of active injections (9.5 and 8.5, respectively) compared with the 2q4 group (11.7 active injections). The difference was particularly favourable for the 8q8/3 group, corresponding to 3 fewer injections over 64 weeks compared with 2q4. This corresponds to an 8 mg/3 dose being superior to 2 mg in terms of the key secondary endpoint.

The key secondary endpoint was thus achieved.

For QUASAR, up to Week 36 and up to Week 64, concerning the different **secondary efficacy endpoints**, all of them were achieved.

According to the results provided by the Applicant, the gain of ≥15 letters from baseline at Week 36, the proportions of participants who gained at least 15 letters in BCVA from baseline at Week 36—based

on observed cases (OC) excluding values following intercurrent events (ICE)—were similar in the 2q4 and 8q8/3 groups (59.8% and 58.8%, respectively), while a slightly higher proportion was observed in the 8q8/5 group (64.9%). Furthermore, the proportions of participants who gained at least 15 letters in BCVA from baseline at Week 64—based on observed cases (OC) excluding values following intercurrent events (ICE)—were similar in the 2q4 and 8q8/3 groups (60.4% and 61.7%, respectively), while a slightly higher proportion was observed in the 8q8/5 group (67.1%). These results are consistent with those observed at Week 36.

At Week 36, the proportions of participants achieving an ETDRS score of at least 69 letters (approximately equivalent to 20/40 Snellen), based on observed cases excluding values after intercurrent events (ICE), were numerically higher in the 8q8/3 and 8q8/5 groups (72.7% and 76.2%, respectively) compared to the 2q4 group (67.8%). Also, at Week 64, these proportions of participants achieving an ETDRS score of at least 69 letters (approximately equivalent to 20/40 Snellen), based on observed cases excluding values after intercurrent events (ICE), were numerically higher in the 8q8/3 and 8q8/5 groups (70.4% and 75.4%, respectively) compared to the 2q4 group (70.2%). These results are consistent with those observed at Week 36.

Moreover, at Week 36, the proportion of participants with no retinal fluid in the central subfield was similar between groups. Specifically, 81.2% of participants in the 8q8/3 dosage group and 81.8% in the 8q8/5 dosage group showed absence of retinal fluid. A slightly higher efficacy was observed in the 2q4 dosage group, with 83.7% of participants having no retinal fluid; however, this difference is not clinically meaningful. Also, at Week 64, the proportion of participants with no retinal fluid in the central subfield appeared to vary between groups. From Week 36 onwards, a gradual decline in efficacy was observed over time; however, higher treatment doses appeared more effective than the lowest dose. The 8q8/3 and 8q8/5 groups (76.3% and 71.3%, respectively) showed higher proportions compared to the 2q4 group (66.0%), suggesting better disease control in the 8 mg groups.

Furthermore, concerning the change from baseline in CST at Week 36, based on the results provided by the Applicant, the least squares (LS) mean change from baseline decreases over time was similar across all treatment groups. Thus, these data suggest that, at Week 36, treatment with aflibercept 8 mg Q8 provides similar efficacy compared to aflibercept 2 mg Q4. Also, at Week 64 the estimated differences in LS mean changes in CST from baseline at Week 64 (95% CIs), based on the MMRM in the FAS, were small: -7.4 µm (95% CI: -20.7, 5.9) for 8q8/3 versus 2q4 and 0.5 µm (95% CI: -12.6, 13.5) for 8q8/5 versus 2q4. These results therefore suggest similar efficacy between the groups in terms of CST change at Week 64.

At baseline, the mean NEI-VFQ-25 total scores were comparable across the three treatment groups, ranging from 78.15 to 79.39. Based on the MMRM analysis in the FAS, the estimated differences (95% CI) at Week 64 were: –1.11 points (95% CI: –2.9 to 0.65) for 8q8/3 vs. 2q4, and -0.54 points (95% CI: –2.3 to 1.17) for 8q8/5 vs. 2q4.These results indicate no clinically meaningful differences between the groups. These results are consistent with those observed at Week 36.

Q4 dosing

In the QUASAR study, patients who had their dosing interval reduced to Q4 obtained a visual benefit and also an improvement in mean CST.

3.3. Uncertainties and limitations about favourable effects

RVO:

There are no major uncertainties in relation to the efficacy. The posology as proposed by the Applicant is acceptable.

Q4 dosing:

There are no uncertainties regarding the data provided by the Applicant, the results are conclusive in demonstrating a therapeutic benefit for patients who are refractory to longer dosing intervals for treatment of RVO, nAMD and DME.

3.4. Unfavourable effects

QUASAR study: RVO indication

The safety profile of Aflibercept 8 mg (114.3 mg/mL) up to Week 36 and Week 64 in RVO (CRVO/BRVO/HRVO) indication is comparable to the established profile of Eylea in adults.

For QUASAR, up to Week 36, ocular TEAEs in the study eye were slightly more frequently reported for all 8 mg group (32.0%) compared to 2q4 (28.2%). Most frequently reported ocular TEAEs in the study eye were IOP increased (5.2% in all 8 mg groups vs 1,7% in 2q4 group), Visual acuity reduced (3.4% in all 8 mg group vs 1.3% in 2q4), Cataract 2.5% in all 8 mg group vs 3.0% in 2q4), Vitreous detachment (2.9% in all HD group vs 0.7% in 2q4) and Conjunctival haemorrhage (2.9% in all HD group vs 2.0% in 2q4) were consistent with the known safety profile of Eylea 8 mg. Ocular TEAEs in the study eye were mainly mild to moderate in intensity. Severe ocular TEAEs in the study eye occurred in comparable proportions across treatment groups (2.0% in 2q4 vs 1.0% in all 8 mg) and mostly in single participants except for Cataract in 8q8/5 group. Ocular TEAEs in the study eye related to study injection (6.3% in 2q4 and 10.7% in all 8 mg group), study intervention (2.0% in 2q4 and 3.0% in all HD group) and procedure protocol (1.0% in 2q4 and 1.9% in all HD group) were reported mostly in single participants which is in line with the known safety profile. Up to Week 64, ocular TEAEs in the study eye were reported in similar proportions between all 8 mg (42.6%) and 2q4 arm (42.2%) and similar tendencies in term of reported PT, seriousness and intensity were observed.

Non-ocular TEAEs were reported in similar proportions up to Week 36 (49.1% in all 8 mg group and 50.2% in 2q4) and up to Week 64 arms (62.8% in 2q4 and 62.3% in all 8 mg) with the most reported PT being Hypertension with the cases being non-serious, assessed as not related to study intervention and almost all were mild or moderate intensity. No clinically relevant changes in BP measurements were observed and no relevant differences were seen across the treatment arms through Weeks 36 and 64. Up to Week 64, severe non-ocular TEAEs occurred in low proportions in both treatment groups (7.3% in 2q4 arm and 6.4% in all 8 mg). Non-ocular TEAEs assessed as related to study intervention were low (0.3% in 2q4 and 0.5% in all 8 mg up to Week 36).

Serious ocular TEAEs in the study eye were low and higher in 2q4 (2.3% vs 1.2% in all 8 mg group). Similarly, up to Week 64, ocular TESAE in the study eye occurred in low proportions, 2.7% participants in 2q4 arm and 1.7% in all 8 mg group. All events were reported in single participants across treatment groups except Endophthalmitis, Visual acuity reduced and Macular Hole. Serious ocular TEAEs were mostly moderate to severe. Serious ocular TEAEs related to study intervention and injection related were low. Serious non-ocular TEAEs were comparable between treatment arms and moderate to severe in intensity. None of the non-ocular serious TEAEs was assessed to be related to study intervention or IVT injection procedure.

AESI were reported in higher proportions in the 2q4 group (3.0% vs 1.0% in all 8 mg group) and mainly in single participants.

Ocular TEAEs in the study eye and non-ocular TEAEs leading to study intervention discontinuation were low and comparable between treatment arms up to Week 36 and Week 64.

Through Week 36, 7 deaths occurred in comparable proportions between treatment arms (0.7% in 2q4 and 8q8/3 and 1.0% in 8q8/5 group). Deaths were reported in 3 additional patients in the 2q4 arm (1.0%) and 7 patients in the all 8 mg group (1.2%) up to Week 64. None of the deaths were assessed as related to study intervention or study procedure.

Q4 safety dosing

Safety data from PULSAR and PHOTON support a favourable safety profile, allowing the maintenance interval to be reduced from 2 months (q8) to 1 month (q4) based on the treating physician's judgement of visual and/or anatomic outcomes for patients in need of a more intense treatment.

In PULSAR, through Week 12 (the end of the loading phase with monthly injections), ocular TEAEs in the study eye were reported in similar proportions between treatment arms (17.3% in 2q8 and 18.1% in all HD). These events are either listed in the SmPC of Eylea or common ocular condition. Ocular study drug related TEAEs were slightly more reported in all HD group (2.2% vs 0.9% in 2q8) but were reported in single participants except for retinal haemorrhage and retinal pigment epithelial tear which are known common AEs of Aflibercept. Ocular TEAEs were mild to moderate in intensity. Ocular serious TEAEs were reported in similar proportions. Ocular safety topics in the study eye were reported in comparable proportions. Cases of IOP increased were all non-serious and without sustained IOP elevations. Non-ocular TEAEs were reported in higher proportion in the HD arms (22.1%) than in 2q8 arm (16.7%) however majority of the PT were reported in single participants and events were consistent with the elderly population. Systemic safety topics, the incidence between 2 mg and 8 mg treated patients were low and comparable.

In PHOTON, through Week 12, ocular TEAEs in the study eye in the initiation phase were higher in HD groups compared to 2q8 (17.1% vs 9.6%) however this difference may be driven by a lower rate in the 2q8 arm in PHOTON during the treatment initiation than in PULSAR. Reported events were mostly observed in single participants and are known ADR or Eylea which are either known as injection related (Vitreous detachment, cataract/cataract cortical and Conjunctival haemorrhage) or also seen in higher proportion in the fellow eye (photopsia and punctuate keratitis). Study drug related ocular TEAEs occurring during the initial monthly dosing phase were reported mostly in single participants except intraocular pressure increased and in low proportions (0.6% in 2q8 and 1.2% in all HD group). Serious ocular TEAEs occurred in single participant and were reported in similar proportions (0.6% in 2q8 and 0.4% in all HD group). None were considered related to the study drug. Ocular TEAEs were mild to moderate in intensity. The incidence rates for safety topics assessed as study drug related were low (less than 1%) and were reported in single participants except for IOP increased and IOI. Non-ocular TEAEs in PHOTON were reported mostly in single participants or were common conditions in the DME population and/or not considered related to an intravitreal anti-VEGF effect. Non-ocular serious TEAEs were more reported in all HD group but no differences above 1% were seen between SOC and none were considered as related to study drug. Severe non-ocular TEAEs were reported in few participants and mostly observed in single participants, none were assessed as related to study drug. Non-ocular study drug related TEAEs during the initial monthly dosing phase occurred in only one patient. Non-ocular safety topics were reported in similar or comparable proportions.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 146: Effects Table for Eylea 114.3 mg/ml for RVO through Week 64

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects					
BCVA at Week 36 (primary efficacy endpoint)	Change from baseline in the study eye at Week 36	Letters LS mean (SE)	8q8/3: 17.4 (0.7) 8q8/5: 18.3 (0.6)	2q4: 17.5 (0.7)	Statistically significant (non-inferiority)
BCVA at Week 64	Change from baseline in the study eye at Week 64	Letters LS mean (SE)	8q8/3: 17.8 (0.7) 8q8/5: 18.1 (0.8)	2q4: 17.3 (0.8)	Descriptive
Number of injections Week 64 (Key secondary endpoint)		LS mean (SE)	8q8/3:8.5 (0.1) 8q8/5: 9.5 (0.1)	2q4: 11.7 (0.1)	Statistically significant (superiority)
Unfavourable Effects (1)					
Ocular TEAE		%	42.6	42.2	
	Conjunctival haemorrhage	%	4.4	2.7	Most frequently reported known ADR of Eylea related to injection procedure
	Retinal haemorrhage	%	1.0	0.3	Most frequently reported known ADR of Eylea
	IOP increased	%	5.9	2.7	Most frequently reported known ADR of Eylea related to injection procedure
	Cataract	%	4.9	5.6	Most frequently reported known ADR of Eylea related to injection procedure
	Visual acuity reduced	%	4.2	4.0	Most frequently reported known ADR of Eylea
	Vitreous detachment	%	3.2	1.3	Most frequently reported known ADR of Eylea related to injection procedure
Non-ocular TEAE	Hypertension	%	9.5	5.0	Most frequently reported non-ocular TEAE and Uncertainties on systemic exposure

Abbreviations: RVO - retinal vein occlusion

Notes: QUASAR 64 Weeks results (2q4 and All HD groups)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Concerning the efficacy profile of Eylea 8 mg in the RVO indication, at Week 64 the primary and secondary data are achieved.

The safety profile of Eylea 8 mg in the RVO indication showed to be in line with the known safety of Eylea. The Week 12 safety data of Eylea 8 mg in nAMD and DME indications were in support of a favourable safety profile for the patients which may be in need of more intensive treatment for the maintenance phase in accordance with the physician's judgement of visual and/or anatomic outcomes.

3.7.2. Balance of benefits and risks

The efficacy profile of Aflibercept 8 mg on the primary endpoint tends to support non-inferiority of both 8mg/5 and 8mg/3 vs 2 mg regimen. Concerning the Q4 dosing, the Applicant provided clarifications, and these were found convincing. In this sense, the B/R balance is positive.

The safety profile of Aflibercept 8 mg (114.3 mg/mL) up to week 36 and week 64 in RVO (CRVO/BRVO/HRVO) indication appears comparable to the already established profile of Eylea in adults. Safety data from PULSAR and PHOTON were in favour of favourable safety profile, allowing a shorter treatment interval of 1 month (q4) instead of 2 months (q8) for the maintenance phase in accordance with the physician's judgement of visual and/or anatomic outcomes for patient in need of a more intense treatment.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Eylea 8 mg is positive in the proposed RVO indication and treatment regimen is positive concerning RVO treatment. Concerning the q4 dosing, the B/R is also positive in patients undergoing treatment for RVO, DME and nAMD.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II	I, and IIIB
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I, and IIIB

A grouped application comprised of two Type II variations, as follows: C.I.6.a: Extension of indication for Eylea 114.3 mg/ml to include the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch, central and hemiretinal retinal vein occlusion, RVO), based on results from study 22153 (QUASAR); this is a randomized, double-masked, active-controlled Phase 3 study of the efficacy and safety of aflibercept 8 mg in macular oedema secondary to retinal vein occlusion. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordingly. The RMP version 36.1 has also been submitted. C.I.4: Update of section 4.2 of the SmPC for Eylea 114.3 mg/ml in order to change posology recommendations of the approved indications neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) based on the results from study 22153 (QUASAR) and post-hoc analysis of the pivotal studies 20968 (PULSAR), 21091 (PHOTON) and Phase II study 21086 (CANDELA).

The group of variations leads to amendments to the annex(es) I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH has agreed to provide EU educational material for Eylea. Prior to launch and during the product's lifecycle in each Member State the MAH will agree the final educational material with the National Competent Authority.

The MAH ensures that, following discussions and agreement with the National Competent Authorities in each Member State where Eylea is marketed, ophthalmological clinics where Eylea is expected to be used are provided with an updated physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs (for adult population only)

The physician information in the educational material contains the following key elements:

- Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
- The vial and the pre-filled syringe are for single use only
- The need to expel excess volume of the syringe before injecting Eylea to avoid overdose (in adult population only)
- Patient monitoring after intravitreal injection including monitoring for visual acuity and increase of intraocular pressure post-injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea (in adult population only)

The following key elements are specific to the ROP (retinopathy of prematurity) indication:

- Use of the paediatric dosing device is mandatory
- The need to properly prime the paediatric dosing device before injection
- The paediatric dosing device is for single use only

The patient information pack of the educational material for the adult population includes a patient information guide and its audio version. The patient information guide contains following key elements:

- Patient information leaflet
- Who should be treated with Eylea
- How to prepare for Eylea treatment
- What are the steps following treatment with Eylea
- Key signs and symptoms of serious adverse events including endophthalmitis, intraocular inflammation, intraocular pressure increased, retinal pigment epithelial tear and cataract
- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Eylea-H-C-00002392-II-EMAVR0000264981'

Attachments

1. SmPC, Package Leaflet (changes highlighted), as adopted by the CHMP on 11 December 2025.