SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Eylea 114.3 mg/ml solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 114.3 mg aflibercept*.

Each pre-filled syringe contains 21 mg aflibercept in 0.184 ml solution. This provides a usable amount to deliver a single dose of 0.07 ml containing 8 mg aflibercept.

* Aflibercept is a fusion protein consisting of portions of human VEGF (vascular endothelial growth factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

Excipient with known effect

Each ml solution for injection contains 0.3 mg polysorbate 20 (E 432).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to slightly opalescent, colourless to pale yellow, iso-osmotic solution, pH 5.8.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Eylea is indicated in adults for the treatment of

- neovascular (wet) age-related macular degeneration (nAMD) (see section 5.1)
- visual impairment due to diabetic macular oedema (DMO) (see section 5.1)
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch, central and hemiretinal RVO) (see section 5.1).

4.2 Posology and method of administration

Eylea must only be administered by a qualified healthcare professional experienced in intravitreal injections.

Posology

nAMD and DMO

The recommended dose is 8 mg aflibercept, equivalent to 0.07 ml solution. The posology is the same for the nAMD and DMO indications. The 8 mg dose requires use of Eylea 114.3 mg/ml.

For patients who are initiating treatment, Eylea is administered with 1 injection per month for 3 consecutive doses. Injection intervals may then be extended up to every 4 months based on the physician's judgement of visual and/or anatomic outcomes. Subsequently, the treatment intervals may be further extended up to 6 months, such as with a treat-and-extend dosing regimen, while maintaining stable visual and/or anatomic outcomes (see section 5.1).

For patients who have previously been treated with Eylea 40 mg/ml or other anti-VEGF medicinal products and are switching to Eylea 114.3 mg/ml, the treatment regimen can differ from that used for treatment-naïve patients. Treatment intervals should be determined based on visual and/or anatomic outcomes (see section 5.1).

- In patients with stable visual and anatomic outcomes, previous treatment intervals can be maintained or extended after the first injection of Eylea 114.3 mg/ml, such as with a treat-and-extend dosing regimen.
- In patients with suboptimal visual and/or anatomic outcomes, treatment with Eylea 114.3 mg/ml may begin with 1 injection per month for up to 3 consecutive doses followed by adjustment of injection intervals, such as with a treat-and-extend dosing regimen.

If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly based on the physician's discretion. 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.

Eylea at monthly doses of 8 mg has not been studied for more than 3 consecutive doses in the PULSAR (nAMD) and PHOTON (DMO) studies. Available data support the administration of more than 3 consecutive monthly doses for certain patients, however the data are currently limited.

The frequency of monitoring visits should be based on the patient's status and at the physician's discretion. For events in which treatment should be withheld see section 4.4.

RVO

The recommended dose is 8 mg aflibercept, equivalent to 0.07 ml solution. The 8 mg dose requires use of Eylea 114.3 mg/ml.

For patients who are initiating treatment, Eylea is administered with 1 injection per month for 3 consecutive doses. Injection intervals may then be extended based on the physician's judgement of visual and/or anatomic outcomes (see section 5.1).

For patients who have previously been treated with Eylea 40 mg/ml or other anti-VEGF medicinal products and are switching to Eylea 114.3 mg/ml, the treatment regimen can differ from that used for treatment-naïve patients. Treatment intervals should be determined based on visual and/or anatomic outcomes (see section 5.1).

- In patients with stable visual and anatomic outcomes, previous treatment intervals can be maintained or extended after the first injection of Eylea 114.3 mg/ml, such as with a treat-and-extend dosing regimen.
- In patients with suboptimal visual and/or anatomic outcomes, treatment with Eylea 114.3 mg/ml may begin with 1 injection per month for up to 3 consecutive doses followed by adjustment of injection intervals, such as with a treat-and-extend dosing regimen.

If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly based on the physician's discretion (see section 5.1). 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.

The frequency of monitoring visits should be based on the patient's status and at the physician's discretion. For events in which treatment should be withheld see section 4.4.

Special populations

Renal or hepatic impairment
No specific studies in patients with renal or hepatic impairment have been conducted. Available data do not suggest a need for a dose adjustment with Eylea in these patients (see section 5.2).

Elderly
Available data do not suggest a need for a dose adjustment with Eylea in these patients.

Paediatric population

The safety and efficacy of Eylea 114.3 mg/ml in children and adolescents below 18 years have not been established. There is no relevant use of Eylea 114.3 mg/ml in the paediatric population in the nAMD, DMO and RVO indications.

Method of administration

Eylea is for intravitreal injection only.

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified healthcare professional experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended.

The injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.07 ml is then delivered. A different scleral site should be used for subsequent injections.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each pre-filled syringe should only be used for the treatment of a single eye.
After injection, discard any unused product or waste material in accordance with local requirements.

For handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Ocular or periocular infection.
- Active severe intraocular inflammation.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Intravitreal injection-related reactions

Intravitreal injections, including those with Eylea, have been associated with endophthalmitis, intraocular inflammation, retinal detachment, retinal tear and traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering Eylea. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay and should be managed appropriately.

Intraocular pressure increased

Transient increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection, including those with Eylea (see section 4.8). Both the intraocular pressure and perfusion of the optic nerve head must therefore be monitored and managed appropriately. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea while the intraocular pressure is $\geq$ 30 mmHg).

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with aflibercept (see section 5.1). Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

Systemic effects

Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition (see section 4.8).
There are limited data on safety in the treatment of patients with nAMD, DMO and RVO with a history of stroke, transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients.

Bilateral treatment

The safety and efficacy of bilateral treatment with Eylea 114.3 mg/ml per eye have not been studied (see section 5.1). If bilateral treatment is performed at the same time this could lead to an increased systemic exposure, which could increase the risk of systemic adverse events.

Concomitant use of other anti-VEGF

There are limited data available on the concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular).

Withholding treatment

Treatment should be withheld in the event of:

- a decrease in best corrected visual acuity (BCVA) of ≥ 30 letters compared with the last assessment of visual acuity
- a rhegmatogenous retinal detachment or stage 3 or 4 macular holes
- a retinal break
- a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥ 50 % of the total lesion area
- performed or planned intraocular surgery within the previous or next 28 days.

Retinal pigment epithelial tear

Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for nAMD include a large and/or high pigment epithelial retinal detachment. When initiating aflibercept therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment and for at least 4 months after the last intravitreal injection with Eylea 114.3 mg/ml (see section 4.6).

Populations with limited data

There is only limited experience with Eylea treatment in diabetic patients with an HbA1c over 12 % or with proliferative diabetic retinopathy.
Eylea has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Eylea in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

Information about excipients

This medicinal product contains 0.021 mg of polysorbate 20 in each 0.07 ml dose which is equivalent to 0.3 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment and for at least 4 months after the last intravitreal injection with Eylea 114.3 mg/ml.

Pregnancy

There are limited data on the use of aflibercept in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Eylea 114.3 mg/ml should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Breast-feeding

Based on very limited human data, aflibercept may be excreted in human milk at low levels. Aflibercept is a large protein molecule and the amount of medication absorbed by the infant is expected to be minimal. The effect of aflibercept on a breast-fed newborn/infant is unknown.

As a precautionary measure breast-feeding is not recommended during the use of Eylea 114.3 mg/ml.

Fertility

There are no fertility data in humans. Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Injection with Eylea has minor influence on the ability to drive and use machines due to possible temporary visual disturbance associated either with the injection or eye examination. Patients should not drive or use machines until their visual function has recovered sufficiently.

4.8 Undesirable effects

Summary of the safety profile

Serious adverse reactions were cataract (7.1%), intraocular pressure increased (3.8%), retinal haemorrhage (2.8%), vitreous haemorrhage (1.1%), cataract subcapsular (0.6%), retinal tear (0.5%), cataract nuclear (0.4%) and retinal detachment (0.4%).

The most frequently observed adverse reactions in patients treated with Eylea 114.3 mg/ml were cataract (7.1%), visual acuity reduced (4.3%), conjunctival haemorrhage (4.0%), intraocular pressure increased (3.8%), vitreous detachment (3.5%), vitreous floaters (3.2%) and retinal haemorrhage (2.8%).

The safety profile observed in the 4 clinical studies was similar in patients treated with Eylea 114.3 mg/ml (N=1 808) and Eylea 40 mg/ml (N=857), and in patients with nAMD, DMO and RVO.

Tabulated list of adverse reactions

A total of 1 808 patients treated with Eylea 114.3 mg/ml up to 96 weeks constituted the safety population in 4 clinical phase II/III studies (CANDELA, PULSAR, PHOTON, QUASAR).
The safety data described below include all adverse reactions with a reasonable possibility of causality to the injection procedure or medicinal product reported.

The adverse reactions are listed by system organ class and frequency using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: All treatment-emergent adverse reactions reported in patients with nAMD, DMO or RVO treated with Eylea 114.3 mg/ml in phase II/III studies or during post marketing surveillance

System organ class	Frequency	Adverse reaction
Immune system disorders	Common	Hypersensitivity*
Eye disorders	Common	Cataract, Intraocular pressure increased, Vitreous floaters, Vitreous detachment, Vitreous haemorrhage, Retinal haemorrhage, Visual acuity reduced, Eye pain, Conjunctival haemorrhage, Punctate keratitis, Corneal abrasion
	Uncommon	Retinal detachment, Retinal tear, Retinal pigment epithelial tear, Detachment of the retinal pigment epithelium, Uveitis, Iritis, Iridocyclitis, Vitritis, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Vision blurred, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Injection site haemorrhage,

		Conjunctival hyperaemia, Lenticular opacities, Eyelid oedema, Ocular hyperaemia, Injection site irritation, Retinal degeneration, Corneal oedema
	Rare	Blindness, Endophthalmitis, Eyelid irritation
	Not known	Scleritis**

* Reports of hypersensitivity included rash, pruritus, urticaria.
** From post marketing reporting.

The following adverse reactions of Eylea 40 mg/ml are also considered expected with Eylea 114.3 mg/ml: abnormal sensation in eye, corneal epithelium defect, anterior chamber flare, traumatic cataract, hypopyon, severe anaphylactic/anaphylactoid reactions.

Description of selected adverse reactions

Product-class-related adverse reactions
Arterial thromboembolic events (ATEs) are adverse reactions potentially related to systemic VEGF inhibition. There is a theoretical risk of ATEs, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. A low incidence rate of ATEs was observed in the aflibercept clinical studies in patients with nAMD, DMO and RVO. Across indications, no notable difference between the groups treated with Eylea 114.3 mg/ml and the comparator groups treated with Eylea 40 mg/ml were observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdose, intraocular pressure should be monitored and, if deemed necessary by the treating physician, adequate treatment should be initiated (see sections 4.4 and 6.6).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals / Antineovascularisation agents, ATC code: S01LA05

Aflibercept 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 is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

Mechanism of action

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 act independently to activate the VEGFR-1 to promote an inflammatory response within the retina, and is known to increase in pathological states such as nAMD, diabetic retinopathy (DR), DMO, and retinal vein occlusion (RVO).

Pharmacodynamic effects

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.
In animal studies, aflibercept can prevent pathological neovascularization and vascular leakage in a number of different models of ocular disease.

nAMD

nAMD is characterised by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid from CNV may cause retinal oedema and/or sub-/intra-retinal haemorrhage, resulting in loss of visual acuity.

The pharmacodynamic effects of aflibercept 114.3 mg/ml administered every 12 (8Q12) and every 16 (8Q16) weeks are described in comparison with aflibercept 40 mg/ml administered every 8 weeks (2Q8) for the nAMD indication. These effects are shown as the change in CNV size from baseline to week 12; change in total lesion area from baseline to weeks 48, 60 and 96; and change from baseline in central retinal thickness (CRT).

In the pooled group of patients treated with 8Q12 or 8Q16, reductions in CNV size (LS mean, based on a mixed model for repeated measurements [MMRM]) at week 12 were -1.63 mm^2 compared to -1.17 mm^2 for patients treated with 2Q8.

Pharmacodynamic effects were generally maintained through week 156.

Table 2: Pharmacodynamic parameter (full analysis set) in the PULSAR study

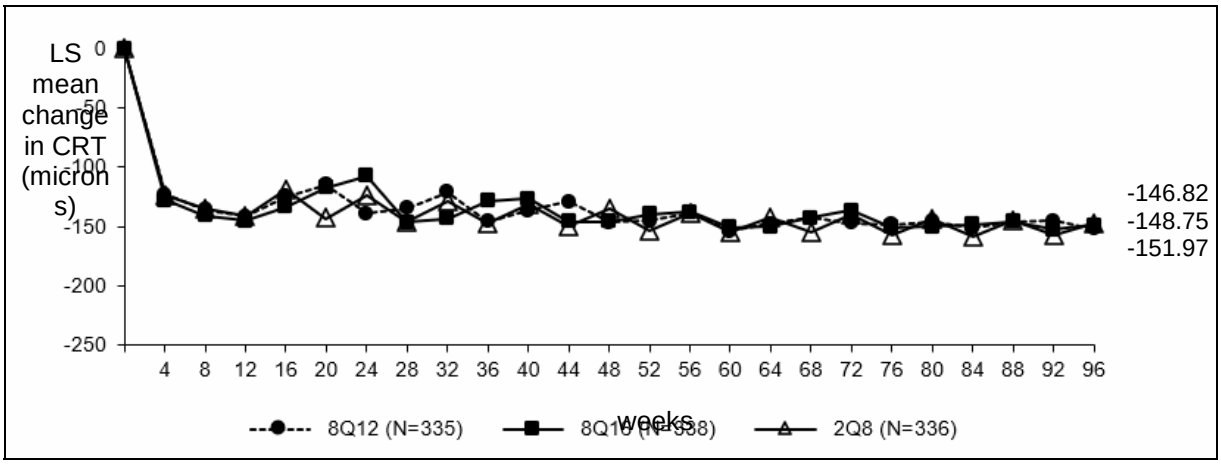
Efficacy outcomes	Week	Eylea 8Q12 (N = 335)	Eylea 8Q16 (N = 338)	Eylea 2Q8 (N = 336)
Change in total lesion area from baseline [mm^2]				
LS mean [A]	12	-0.55		-0.30
Arithmetic mean (SD), observed	48	-0.4 (2.9)	-0.2 (3.1)	0.1 (3.6)
LS mean (SE) [A]		-0.46 (0.19)	-0.35 (0.20)	0.09 (0.22)
Difference in LS means (95% CI) [A,B]		-0.55 (-1.04, -0.06)	-0.44 (-0.94, -0.06)	
Arithmetic mean (SD), observed	60	-0.5 (2.8)	-0.4 (3.2)	-0.3 (3.2)
LS mean (SE) [A]		-0.48 (0.20)	-0.54 (0.21)	-0.24 (0.20)
Difference in LS means (95% CI) [A,B]		-0.24 (-0.72, 0.24)	-0.29 (-0.79, 0.20)	
Arithmetic mean (SD), observed	96	-0.3 (3.3)	-0.3 (3.2)	-0.2 (3.4)
LS mean (SE) [A]		-0.43 (0.20)	-0.42 (0.20)	-0.18 (0.20)
Difference in LS means (95% CI) [A,B]		-0.25 (-0.72, 0.21)	-0.24 (-0.71, 0.22)	

[A] LS mean, CI and p-value based on an MMRM with baseline measurement as covariate, treatment group as factor, visit and stratification variables used for randomisation (geographical region, categorical baseline BCVA) as fixed factors as well as terms for the interaction between baseline measurement and visit and for the interaction between treatment and visit.

[B] Absolute difference is Eylea 8Q12- or 8Q16-groups minus 2Q8-groups, respectively.

CI: Confidence interval
LS: Least square
SD: Standard deviation
SE: Standard error

Figure 1: LS mean change in central retinal thickness (CRT) from baseline through week 96 (full analysis set) in the PULSAR study



DMO

Diabetic macular oedema is characterised by increased vasopermeability and damage to the retinal capillaries which may result in loss of visual acuity.

The pharmacodynamic effects of aflibercept 114.3 mg/ml administered every 12 (8Q12) and every 16 (8Q16) weeks are described in comparison with aflibercept 40 mg/ml administered every 8 weeks (2Q8) for the DMO indication. These effects are shown as the change in the leakage area from baseline to weeks 48, 60 and 96.

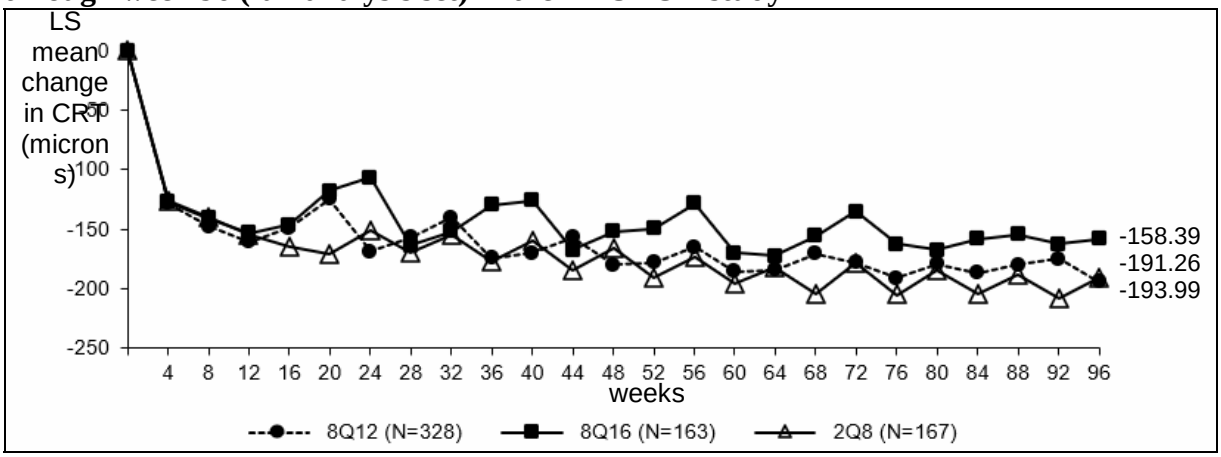
Pharmacodynamic effects were generally maintained through week 156.

Table 3: Pharmacodynamic parameter (full analysis set) in the PHOTON study

Efficacy Outcomes	**Week**	**Eylea 8Q12 (N = 328)**	**Eylea 8Q16 (N = 163)**	**Eylea 2Q8 (N = 167)**
Change in leakage area[A] from baseline [mm^2]				
Arithmetic mean (SD), observed	48	-13.9 (13.91)	-9.4 (11.50)	-9.2 (12.11)
	60	-13.9 (13.54)	-12.0 (13.26)	-14.4 (12.89)
	96	-12.8 (10.98)	-9.4 (10.61)	-11.9 (11.26)

[A] based on fluorescein angiography measurement
SD: Standard deviation

Figure 2: LS mean change in central retinal thickness (CRT) from baseline through week 96 (full analysis set) in the PHOTON study



Immunogenicity
After dosing with Eylea 114.3 mg/ml for up to 96 weeks treatment-emergent antibodies to Eylea 114.3 mg/ml were detected in 2.5% to 4.4% of patients treated for DMO and nAMD. No evidence of anti-drug antibodies impact on pharmacokinetics, efficacy or safety was observed.

RVO

In RVO, retinal ischaemia occurs and signals the release of VEGF which in turn destabilises the tight junctions and promotes endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood retina barrier and

this increased vascular permeability results in retinal oedema, stimulation of endothelial cell growth and neovascularisation.

Table 4: Pharmacodynamic parameter (full analysis set) in the QUASAR study

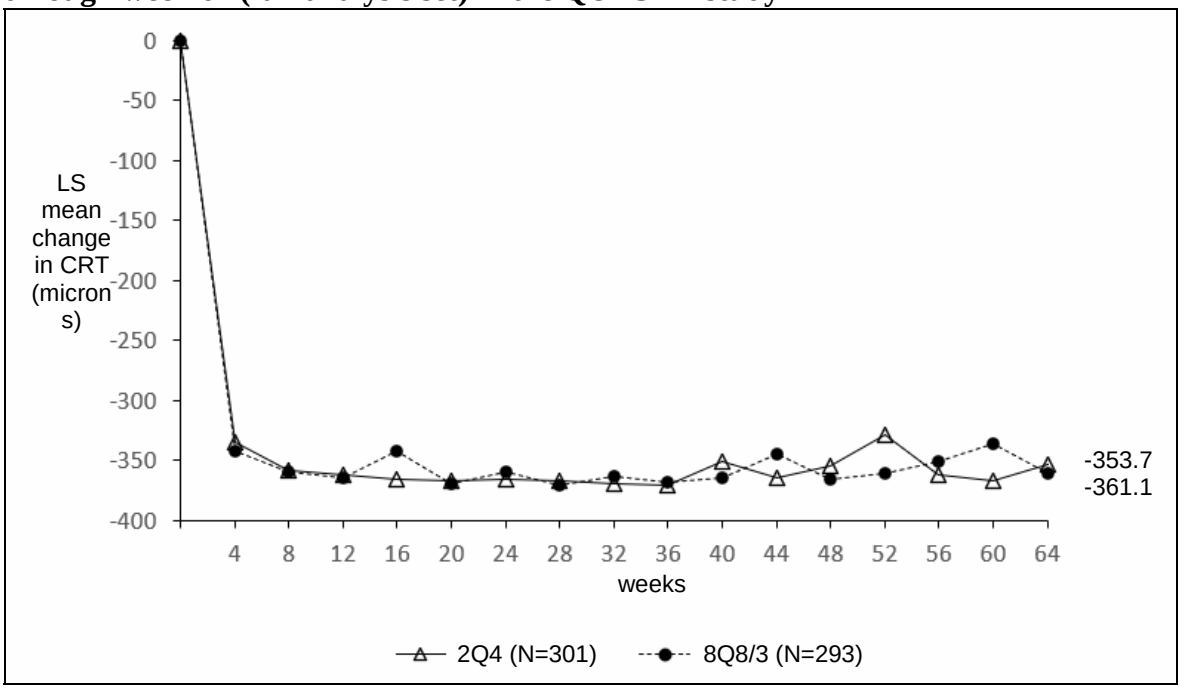
Efficacy outcomes	**Week**	**Eylea 8Q8/3 (N = 293)**	**Eylea 2Q4 (N = 301)**
Change in CRT from baseline [microns]			
Arithmetic mean (SD), observed	36	-365.9 (239.9)	-397.3 (257.7)
LS mean (SE) [A]		-370.9 (3.1)	-370.8 (3.9)
Difference in LS means (95% CI) [A,B]		-0.1 (-10.0, 9.8)	
Arithmetic mean (SD), observed	64	-355.5 (239.5)	-373.0 (252.1)
LS mean (SE) [A]		-361.1 (4.3)	-353.7 (5.2)
Difference in LS means (95% CI) [A,B]		-7.4 (-20.7, 5.9)	

[A] LS mean, CI and p-value based on an MMRM with baseline CRT measurement as covariate, treatment group as factor, visit and stratification variables used for randomisation (geographical region, categorical baseline BCVA and RVO type) as fixed factors as well as terms for the interaction between baseline CRT and visit and for the interaction between treatment and visit.

[B] Absolute difference is Eylea 8Q8/3-group minus 2Q4-group.

CI: Confidence interval
CRT: Central retinal thickness
LS: Least square
SD: Standard deviation
SE: Standard error

Figure 3: LS mean change in central retinal thickness (CRT) from baseline through week 64 (full analysis set) in the QUASAR study



Clinical efficacy and safety

nAMD

Study objectives

The safety and efficacy of Eylea 114.3 mg/ml were assessed in a randomised, multi-centre, double-masked, active-controlled study (PULSAR) in patients with treatment naïve nAMD.

The primary objective was to determine if treatment with Eylea 114.3 mg/ml at intervals of 12 (8Q12) or 16 weeks (8Q16) provides non-inferior best corrected visual acuity (BCVA) change compared to Eylea 40 mg/ml every 8 weeks in patients with nAMD.
The secondary objectives were to determine the effect of Eylea 114.3 mg/ml versus Eylea 40 mg/ml on anatomic and other visual measures of response, and to evaluate the safety, immunogenicity, and pharmacokinetics of aflibercept.

The primary efficacy endpoint was the change from baseline in BCVA measured by the early treatment diabetic retinopathy study (ETDRS) letter score at week 48.
The key secondary endpoints were the change in BCVA from baseline at week 60 and the proportion of patients with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in central subfield at week 16.
Further secondary endpoints were the proportion of patients gaining at least 15 letters in BCVA from baseline at week 48, the proportion of patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at week 48, and the change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at week 48, among others.

In the PULSAR study a total of 1 009 patients were treated. The patients were assigned in a 1:1:1 ratio to 1 of 3 parallel treatment groups:
1. Eylea 114.3 mg/ml administered every 12 weeks (8Q12)
2. Eylea 114.3 mg/ml administered every 16 weeks (8Q16)
3. Eylea 40 mg/ml administered every 8 weeks (2Q8)

All patients received 3 initial injections of the assigned dose at 4-week intervals.
Per study protocol the interval of the 8Q12- and 8Q16-groups was to be shortened if both of the following criteria were met:
1. >5 letters loss in BCVA from week 12, and
2. >25 microns increase in CRT from week 12 or new foveal haemorrhage or new foveal neovascularisation.

Regardless of whether patient intervals were maintained or shortened in year 1, per study protocol all patients in the 8Q12- and 8Q16-groups were eligible for interval extension (by 4 weeks increments), beginning at week 52, if the following criteria were met:
1. <5 letters loss in BCVA from week 12, and
2. no fluid in the central subfield on optical coherence tomography (OCT), and
3. no new onset of foveal haemorrhage or foveal neovascularisation.

For patients who did not meet the criteria for shortening or extension of the interval, the dosing interval was maintained. The minimum interval between injections was 8 weeks in all groups.
Patients with bilateral disease were eligible to receive Eylea 40 mg/ml treatment or another anti-VEGF medicinal product in their fellow eye.

Patient characteristics at baseline
Patient ages ranged from 50 to 96 years with a mean of 74.5 years.
Approximately 92% (309/335) and 87% (295/338) of the patients randomised to the 8Q12- and 8Q16-groups, respectively, were 65 years of age or older and approximately 51% (172/335) and 51% (171/338) were 75 years of age or older.

Results
Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 48 received a median (mean) of 6.0 (6.1), 5.0 (5.2) and 7.0 (6.9) injections, respectively.
At week 48, in the 8Q12-group, 79.4% of patients maintained Q12 intervals while in the 8Q16-group 76.6% of patients maintained Q16 intervals.
Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 60 received a median (mean) of 7.0 (7.1), 6.0 (6.2) and 9.0 (8.8) injections, respectively.
At week 60, 43.1% of patients in the 8Q12-group were extended to a treatment interval of 16 weeks, and 38.5% of patients in the 8Q16-group were extended to a treatment interval of 20 weeks.
Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 96 received a median (mean) of 9.0 (9.7), 8.0 (8.2) and 13.0 (12.8) injections, respectively.
At week 96, in the pooled 8Q12- and 8Q16-groups 71.0% of patients had attained treatment intervals of ≥16 weeks, 46.8% of patients had attained treatment intervals of ≥20 weeks, and 27.8% of patients had attained treatment intervals of 24 weeks, while maintaining visual and anatomic outcomes.

Treatment with 8Q12 and 8Q16 was shown to be non-inferior and clinically equivalent to treatment with 2Q8 in terms of the primary efficacy endpoint ‘mean change in BCVA at week 48’ and the key secondary efficacy endpoint ‘mean change in BCVA at week 60’. The treatment effect with Eylea 114.3 mg/ml in mean change in BCVA was maintained through week 96.

Furthermore, treatment with Eylea (pooled 8Q12- and 8Q16-groups) was shown to be superior to treatment with 2Q8 in terms of the key secondary efficacy endpoint ‘proportion of patients with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the central subfield at week 16’ (see table 5).

Table 5: Efficacy outcomes from the PULSAR study

Efficacy outcomes	Week	Eylea 8Q12 (N = 335)	Eylea 8Q16 (N = 338)	Eylea 2Q8 (N = 336)
Change in BCVA from baseline as measured by ETDRS letter score [D]				
Arithmetic mean (SD), observed	48	6.7 (12.6)	6.2 (11.7)	7.6 (12.2)
LS mean (SE) [A]		6.06 (0.77)	5.89 (0.72)	7.03 (0.74)
Difference in LS means (95% CI) [A,B]		-0.97 (-2.87, 0.92)	-1.14 (-2.97, 0.69)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [A,B]		0.0009	0.0011	
Arithmetic mean (SD), observed	60	6.6 (13.6)	6.6 (11.7)	7.8 (12.6)
LS mean (SE) [A]		6.37 (0.74)	6.31 (0.66)	7.23 (0.68)
Difference in LS means (95% CI) [A,B]		-0.86 (-2.57, 0.84)	-0.92 (-2.51, 0.66)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [A,B]		0.0002	<0.0001	
Arithmetic mean (SD), observed	96	5.9 (14.2)	5.6 (13.7)	7.4 (13.8)
LS mean (SE) [A]		5.59 (0.77)	5.52 (0.75)	6.60 (0.73)
Difference in LS means (95% CI) [A,B]		-1.01 (-2.82, 0.80)	-1.08 (-2.87, 0.71)	
Patients with no IRF and no SRF in the central subfield [D]				
Proportion (LOCF)	16	63.3%		51.6%
Adjusted difference in proportion (95% CI) [B,C]		11.7% (5.3%, 18.2%)		
p-value (one-sided superiority test) [B, C]		0.0002		
Proportion (LOCF)	48	71.1%	66.8%	59.4%
Adjusted difference in proportion (95% CI) [B,C]		11.7% (4.5%, 18.9%)	7.5% (0.1%, 14.8%)	
Proportion (LOCF)	60	74.6%	72.2%	74.6%
Adjusted difference in proportion (95% CI) [B,C]		0.0% (-6.6%, 6.7%)	-2.2% (-8.9%, 4.4%)	
Proportion (LOCF)	96	69.6%	63.6%	66.5%
Adjusted difference in proportion (95% CI) [B,C]		3.0% (-4.1%, 10.1%)	-3.0% (-10.2%, 4.2%)	
Efficacy outcomes	**Week**	**Eylea 8Q12 (N = 335)**	**Eylea 8Q16 (N = 338)**	**Eylea 2Q8 (N = 336)**
Patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) [D]				
Proportion (LOCF)	48	56.9%	54.3%	57.9%
Adjusted difference in proportion (95% CI) [B,C]		-0.2% (-6.6%, 6.2%)	-2.2% (-8.4%, 4.0%)	
Proportion (LOCF)	60	56.3%	54.6%	58.2%
Adjusted difference in proportion (95% CI) [B,C]		-1.1% (-7.5%, 5.3%)	-2.3% (-8.7%, 4.1%)	
Proportion (LOCF)	96	53.3%	53.1%	56.7%
Adjusted difference in proportion (95% CI) [B,C]		-2.7% (-9.4%, 4.0%)	-2.4% (-9.1%, 4.2%)	
Patients who gained at least 15 letters in BCVA from baseline [D]				
Proportion (LOCF)	48	20.7%	21.7%	22.1%
Adjusted difference in proportion (95% CI) [B,C]		-1.7% (-7.8%, 4.3%)	-0.9% (-7.0%, 5.1%)	
Proportion (LOCF)	60	23.7%	23.1%	23.3%
Adjusted difference in proportion (95% CI) [B,C]		0.1% (-6.2%, 6.3%)	-0.7% (-6.9%, 5.5%)	
Proportion (LOCF)	96	22.2%	22.8%	24.2%
Adjusted difference in proportion (95% CI) [B,C]		-2.4% (-8.4%, 3.6%)	-2.0% (-8.0%, 4.1%)	

Last intended treatment intervals				
Patients at ≥Q12 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	87.8%		n/a
Proportion		86.6%	89.0%	n/a
Patients at ≥Q16 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	71.0%		n/a
Proportion		63.6%	78.4%	n/a
Patients at ≥Q20 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	46.8%		n/a
Proportion		40.5%	53.1%	n/a
Patients at Q24 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	27.8%		n/a
Proportion		24.7%	30.8%	n/a

[A] LS mean, CI and p-value based on an MMRM with baseline best corrected visual acuity (BCVA) measurement as covariate, treatment group as factor, visit and stratification variables used for randomisation (geographical region, categorical baseline BCVA) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.

[B] Absolute difference is Eylea 8Q12- or 8Q16-groups minus 2Q8-groups, respectively.

[C] Mantel-Haenszel weighted treatment difference with stratification variables used for randomization (geographical region, categorical baseline BCVA) and CI calculated using normal approximation.

[D] Full analysis set

[E] Safety analysis set; patients considered as completer for the respective timepoint

CI: Confidence interval

LOCF: Last observation carried forward

LS: Least square

SD: Standard deviation

SE: Standard error

Treatment intervals were analysed in a pre-specified exploratory manner.

Figure 4: LS mean change in BCVA as measured by ETDRS letter score from baseline through week 96 (full analysis set) in the PULSAR study

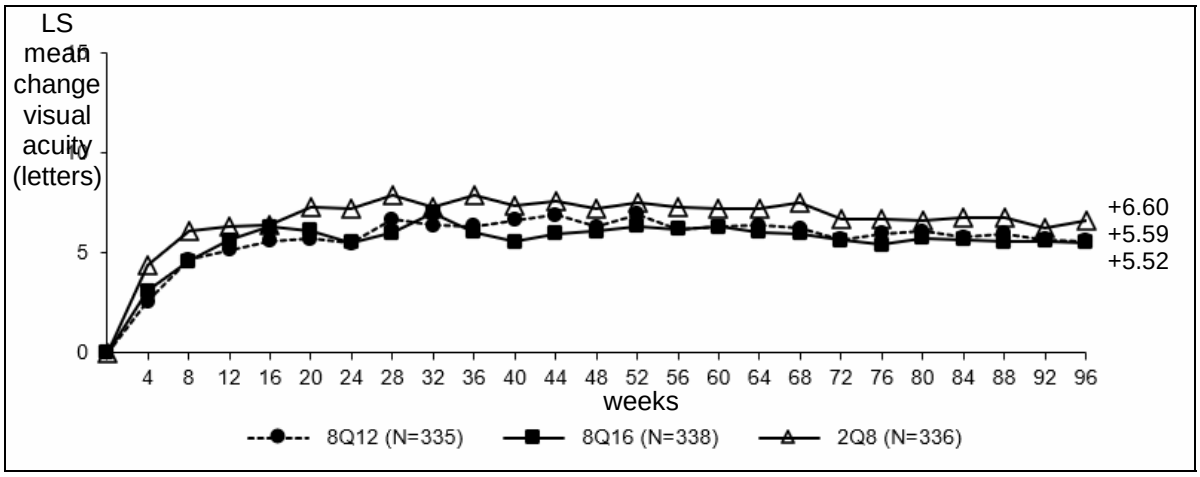
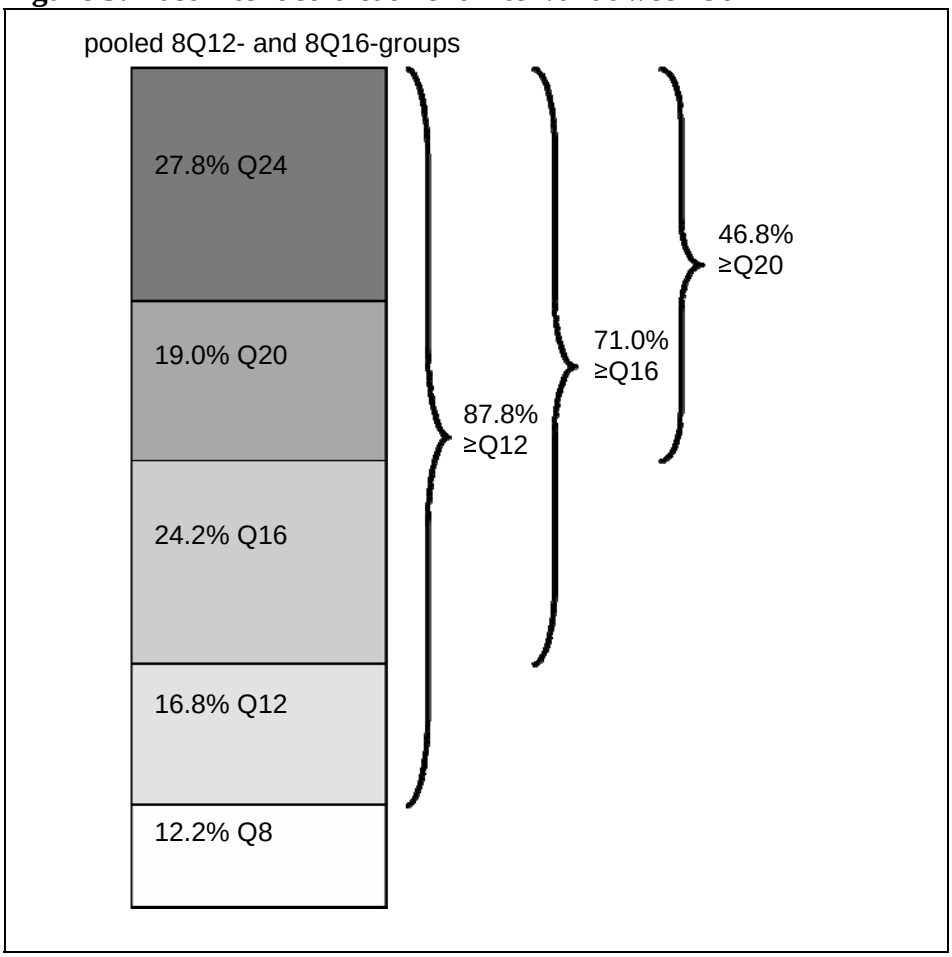


Figure 5: Last intended treatment interval at week 96



Aflibercept at all doses (8Q12, 8Q16, 2Q8) demonstrated meaningful increase from baseline in the pre-specified secondary efficacy endpoint national eye institute visual function questionnaire (NEI VFQ-25).
No clinically meaningful differences were found between the 8Q12-, 8Q16- and 2Q8-groups in changes of NEI VFQ-25 total score at week 48 and week 96 from baseline.

Efficacy results in evaluable subgroups for age, gender, geographic region, ethnicity, race, baseline BCVA, and lesion type were consistent with the results in the overall population.
Efficacy was generally maintained through week 96.

Results - PULSAR extension phase

At the end of the main phase of the study at week 96, patients could enrol into the 60 week, open-label extension phase. 417 patients originally assigned to 8Q12 and 8Q16 continued on Eylea 114.3 mg/ml while maintaining their latest intervals.
208 patients originally assigned to 2Q8 at the beginning of the study were switched to Eylea 114.3 mg/ml starting at 12-week intervals. Treatment intervals could be further adjusted based on the physician's judgement of visual and/or anatomic outcomes.

In those patients originally assigned to 8Q12 and 8Q16, the treatment effect with Eylea 114.3 mg/ml was generally maintained throughout 3 years (week 156). The LS mean change from baseline in the pooled 8Q12- and 8Q16-groups in BCVA was +3.41 letters and in CRT was -148.05 microns at week 156.

In those patients originally assigned to 2Q8, the treatment effect with Eylea 114.3 mg/ml was similar. The LS mean change from baseline in BCVA was +4.58 letters and in CRT was -145.21 microns at week 156.
Patients in the 8Q12- and 8Q16-groups who completed week 156 received a median (mean) of 13.0 (13.5) and 11.0 (12.2) injections, respectively.

Patients who switched to Eylea 114.3 mg/ml and completed week 156 received a total median (mean) of 18.0 (17.7) injections, of which 5.0 (4.9) injections were administered after the switch to Eylea 114.3 mg/ml within the 60 weeks of the study extension phase.

The overall safety profile in the extension phase was similar to that observed in the main phase.

Table 6: Efficacy outcomes from the PULSAR extension phase at week 156

Efficacy outcomes	**8Q12 continued on Eylea 114.3 mg/ml (N = 185)**	**8Q16 continued on Eylea 114.3 mg/ml (N = 190)**	**2Q8 switched to Eylea 114.3 mg/ml (N = 208)**
Change in BCVA from baseline (LS mean)	+3.57 letters	+3.23 letters	+4.58 letters
Change in CRT from baseline (LS mean)	-148.42 microns	-147.54 microns	-145.21 microns
Last intended treatment interval [A]			
≥12 weeks	76.2%	78.4%	78.5%
≥16 weeks	53.5%	62.1%	42.5%
≥20 weeks	37.8%	42.6%	16.1%
24 weeks	23.8%	24.2%	NA [B]

[A] based on patients completing week 156

[B] NA for patients originally randomised to 2Q8, due to study design/length of study

DMO

Study objectives
The safety and efficacy of Eylea 114.3 mg/ml were assessed in a randomised, multi-centre, double-masked, active-controlled study (PHOTON) in patients with DMO.

The primary objective was to determine if treatment with Eylea 114.3 mg/ml at intervals of 12 (8Q12) or 16 weeks (8Q16) provides non-inferior BCVA change compared to Eylea 40 mg/ml every 8 weeks.
The secondary objectives were to determine the effect of Eylea 114.3 mg/ml versus Eylea 40 mg/ml on anatomic and other visual measures of response, and to evaluate the safety, immunogenicity, and pharmacokinetics of aflibercept.

The primary efficacy endpoint was the change from baseline in BCVA measured by the early treatment diabetic retinopathy study (ETDRS) letter score at week 48.
One key secondary endpoint was the change in BCVA from baseline at week 60.
Further secondary endpoints were the proportion of patients gaining at least 15 letters in BCVA from baseline at week 48, the proportion of patients achieving an ETDRS

letter score of at least 69 (approximate 20/40 Snellen equivalent) at week 48, and the change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at week 48, among others.

In the PHOTON study a total of 658 patients were treated. The patients were assigned in a 2:1:1 ratio to 1 of 3 parallel treatment groups:

1. Eylea 114.3 mg/ml administered every 12 weeks (8Q12)
2. Eylea 114.3 mg/ml administered every 16 weeks (8Q16)
3. Eylea 40 mg/ml administered every 8 weeks (2Q8)

Patients who were switched from other anti-VEGF medicinal products to Eylea 114.3 mg/ml received the last injection of the previous treatment at least 12 weeks prior to initiating the Eylea 114.3 mg/ml treatment.

All patients in the 8Q12- and 8Q16-groups received 3 initial injections and all patients in the 2Q8-group received 5 initial injections at 4-week intervals.
Per study protocol the interval of the 8Q12- and 8Q16-groups was to be shortened if both of the following criteria were met:

1. >10 letter loss in BCVA from week 12 in association with persistent or worsening DMO, and
2. >50 microns increase in CRT from week 12.

Regardless of whether patient intervals were maintained or shortened in year 1, per study protocol all patients in the 8Q12- and 8Q16-groups were eligible for interval extension (by 4 weeks increments), beginning at week 52, if the following criteria were met:

1. <5 letter loss in BCVA from week 12, and
2. CRT <300 microns on SD-OCT (or <320 microns if measured including RPE).

For patients who did not meet the criteria for shortening or extension of the interval, the dosing interval was maintained. The minimum interval between injections was 8 weeks in all groups.
Patients with bilateral disease were eligible to receive Eylea 40 mg/ml treatment in their fellow eye.

Patient characteristics at baseline
Patient ages ranged from 24 to 90 years with a mean of 62.3 years.
Approximately 44% (143/328) and 44% (71/163) of the patients randomised to the 8Q12- and 8Q16-groups, respectively, were 65 years of age or older and approximately 11% (36/328) and 14% (14/163) were 75 years of age or older.
The proportion of patients who were treated previously for DMO was balanced between the treatment groups (43.6% in 8Q12-, 43.6% in 8Q16-, 44.3% in 2Q8-group).

Results
Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 48 received a median (mean) of 6.0 (6.0), 5.0 (5.0) and 8.0 (7.9) injections, respectively.
At week 48, in the 8Q12-group, 91.0% of patients maintained Q12 intervals while in the 8Q16-group 89.1% of patients maintained Q16 intervals.
Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 60 received a median (mean) of 7.0 (7.0), 6.0 (6.0) and 10.0 (9.8) injections, respectively. At

week 60, 42.6% of patients in the 8Q12-group were extended to a treatment interval of 16 weeks, and 34.2% of patients in the 8Q16-group were extended to a treatment interval of 20 weeks.
Patients in the 8Q12-, 8Q16- and 2Q8-groups who completed week 96 received a median (mean) of 9.0 (9.5), 8.0 (7.8) and 14.0 (13.8) injections, respectively.
At week 96, in the pooled 8Q12- and 8Q16-groups 72.4% of patients had attained treatment intervals of ≥16 weeks, 44.3% of patients had attained treatment intervals of ≥20 weeks, and 26.8% of patients had attained treatment intervals of 24 weeks, while maintaining visual and anatomic outcomes.

Treatment with Eylea (both 8Q12- and 8Q16-groups) was shown to be non-inferior and clinically equivalent to treatment with 2Q8 in terms of the primary efficacy endpoint ‘mean change in BCVA at week 48’ and the key secondary efficacy endpoint ‘mean change in BCVA at week 60’. The treatment effect with Eylea 114.3 mg/ml in mean change in BCVA was maintained through week 96.

Table 7: Efficacy outcomes from the PHOTON study

Efficacy outcomes	Week	Eylea 8Q12 (N = 328)	Eylea 8Q16 (N = 163)	Eylea 2Q8 (N = 167)
Change in BCVA from baseline as measured by ETDRS letter score [D]				
Arithmetic mean (SD), observed	48	8.77 (8.95)	7.86 (8.38)	9.21 (8.99)
LS mean (SE) [A]		8.10 (0.61)	7.23 (0.71)	8.67 (0.73)
Difference in LS means (95% CI) [A,B]		-0.57 (-2.26, 1.13)	-1.44 (-3.27, 0.39)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [A,B]		<0.0001	0.0031	
Arithmetic mean (SD), observed	60	9.05 (9.27)	7.96 (9.14)	9.62 (9.58)
LS mean (SE) [A]		8.52 (0.63)	7.64 (0.75)	9.40 (0.77)
Difference in LS means (95% CI) [A,B]		-0.88 (-2.67, 0.91)	-1.76 (-3.71, 0.19)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [A,B]		0.0003	0.0122	
Arithmetic mean (SD), observed	96	8.82 (9.93)	7.50 (9.86)	8.41 (11.10)
LS mean (SE) [A]		8.15 (0.63)	6.59 (0.77)	7.70 (0.89)
Difference in LS means (95% CI) [A,B]		0.45 (-1.55, 2.45)	-1.11 (-3.27, 1.05)	
Patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) [D]				
Proportion (LOCF)	48	65.3%	62.6%	63.0%
Adjusted difference in proportion (95% CI) [B,C]		2.45% (-6.47%, 11.36%)	-0.67% (-11.16%, 9.82%)	
Proportion (LOCF)	60	64.7%	62.0%	60.6%
Adjusted difference in proportion (95% CI) [B,C]		4.34% (-4.72%, 13.40%)	1.63% (-8.91%, 12.17%)	
Proportion (LOCF)	96	66.9%	61.3%	63.0%
Adjusted difference in proportion (95% CI) [B,C]		4.01% (-4.99%, 13.01%)	-1.51% (-11.91%, 8.89%)	
Patients who gained at least 15 letters in BCVA from baseline [D]				
Proportion (LOCF)	48	18.7%	16.6%	23.0%
Adjusted difference in proportion (95% CI) [B,C]		-4.64% (-12.30%, 3.02%)	-7.14% (-15.45%, 1.17%)	
Proportion (LOCF)	60	21.5%	16.0%	26.1%
Adjusted difference in proportion (95% CI) [B,C]		-5.01% (-13.04%, 3.02%)	-10.78% (-19.27%, -2.29%)	
Proportion (LOCF)	96	24.5%	19.6%	26.1%
Adjusted difference in proportion (95% CI) [B,C]		-1.88% (-10.03%, 6.28%)	-7.07% (-15.94%, 1.80%)	
Last intended treatment intervals				
Patients at ≥Q12 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	92.9%		n/a
Proportion		91.8%	95.0%	n/a
Patients at ≥Q16 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	72.4%		n/a
Proportion		64.1%	87.8%	n/a
Patients at ≥Q20 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	44.3%		n/a
Proportion		43.0%	46.8%	n/a
Patients at Q24 treatment interval [E]				
Proportion (pooled 8Q12- and 8Q16-groups)	96	26.8%		n/a
Proportion		23.8%	32.4%	n/a

[A] LS mean, CI and p-value based on an MMRM with baseline best corrected visual acuity (BCVA) measurement as covariate, treatment group as factor, visit and stratification variables used for randomisation (geographical region, categorical baseline BCVA) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.

[B] Absolute difference is Eylea 8Q12- or 8Q16-groups minus 2Q8-groups, respectively.

[C] Mantel-Haenszel weighted treatment difference with stratification variables used for randomization (geographical region, categorical baseline BCVA) and CI calculated using normal approximation.

[D] Full analysis set

[E] Safety analysis set; patients considered as completer for the respective timepoint

CI: Confidence interval

LOCF: Last observation carried forward

LS: Least square

SD: Standard deviation

SE: Standard error

Treatment intervals were analysed in a pre-specified exploratory manner.

Figure 6: LS mean change in BCVA as measured by ETDRS letter score from baseline through week 96 (full analysis set) in the PHOTON study

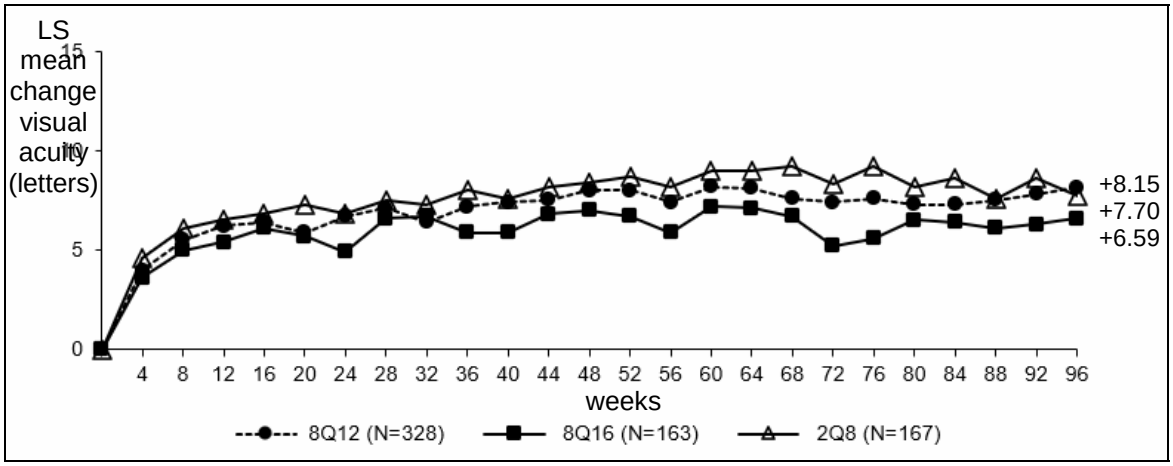
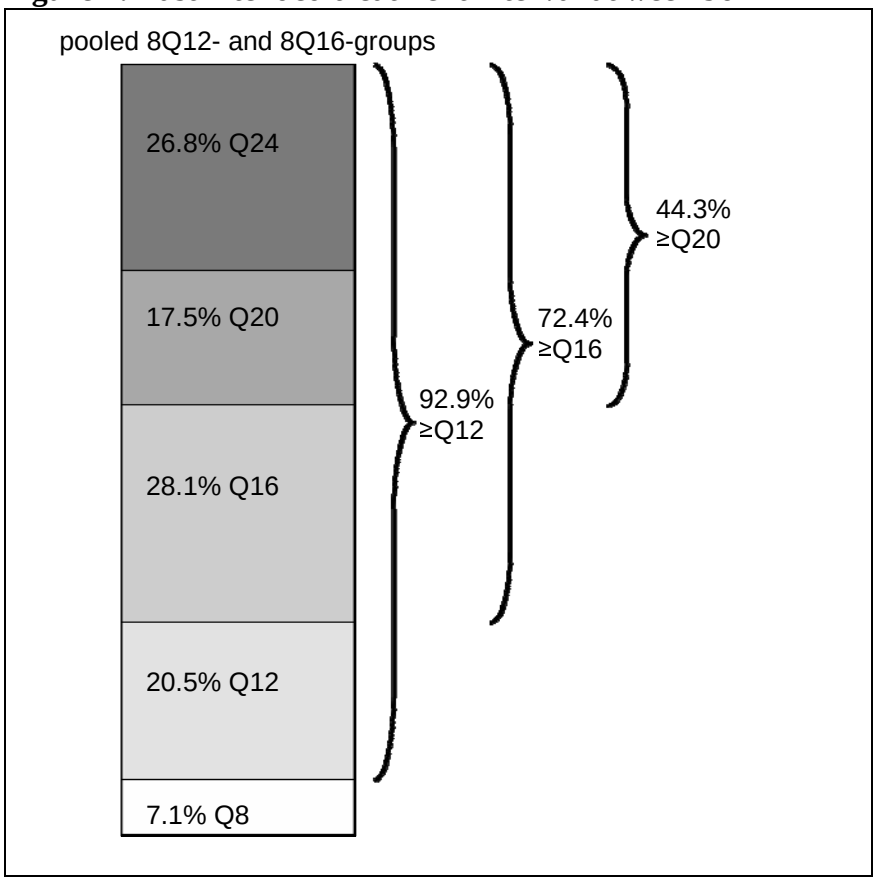


Figure 7: Last intended treatment interval at week 96



Eylea at all doses (8Q12, 8Q16, 2Q8) demonstrated meaningful increase from baseline in the pre-specified secondary efficacy endpoint national eye institute visual function questionnaire (NEI VFQ-25).
No clinically meaningful differences were found between the 8Q12-, 8Q16- and 2Q8-groups in changes of NEI VFQ-25 total score at week 48 and week 96 from baseline.

Efficacy results in evaluable subgroups for age, gender, geographic region, ethnicity, race, baseline BCVA and baseline CRT and prior DMO treatment were consistent with the results in the overall population.
Efficacy was generally maintained through week 96.

Treatment effects in the sub-group of previously treated patients were similar to those seen in patients who were treatment naïve.

Results - PHOTON extension phase

At the end of the main phase of the study at week 96, patients could enrol into the 60 week, open-label extension phase. 195 patients originally assigned to 8Q12 and 8Q16 continued on Eylea 114.3 mg/ml while maintaining their latest intervals.
70 patients originally assigned to 2Q8 at the beginning of the study were switched to Eylea 114.3 mg/ml starting at 12-week intervals. Treatment intervals could be further adjusted based on the physician's judgement of visual and/or anatomic outcomes.

In those patients originally assigned to 8Q12 and 8Q16, the treatment effect with Eylea 114.3 mg/ml was generally maintained throughout 3 years (week 156). The LS mean change from baseline in the pooled 8Q12- and 8Q16-groups in BCVA was +7.2 letters and in CRT was -192.4 microns at week 156.

In those patients originally assigned to 2Q8, the treatment effect with Eylea 114.3 mg/ml was similar. The LS mean change from baseline in BCVA was +6.5 letters and in CRT was -197.4 microns at week 156.

Patients in the 8Q12- and 8Q16-groups who completed week 156 received a median (mean) of 13.0 (13.2) and 11.0 (11.4) injections, respectively.

Patients who switched to Eylea 114.3 mg/ml and completed week 156 received a total median (mean) of 19.0 (18.6) injections, of which 5.0 (4.8) injections were administered after the switch to Eylea 114.3 mg/ml within the 60 weeks of the study extension phase.

The overall safety profile in the extension phase was similar to that observed in the main phase.

Table 8: Efficacy outcomes from the PHOTON extension phase at week 156

Efficacy outcomes	**8Q12 continued on Eylea 114.3 mg/ml (N = 103)**	**8Q16 continued on Eylea 114.3 mg/ml (N = 49)**	**2Q8 switched to Eylea 114.3 mg/ml (N = 70)**
Change in BCVA from baseline (LS mean)	+6.8 letters	+8.1 letters	+6.5 letters
Change in CRT from baseline (LS mean)	-190.3 microns	-198.1 microns	-197.4 microns
Last intended treatment interval [A]			
≥12 weeks	85.4%	91.8%	82.8%
≥16 weeks	62.1%	81.6%	50.0%
≥20 weeks	40.8%	63.3%	19.0%
24 weeks	20.4%	42.9%	NA [B]

[A] based on patients completing week 156

[B] NA for patients originally randomised to 2Q8, due to study design/length of study

RVO

Study objectives

The safety and efficacy of Eylea 114.3 mg/ml were assessed in a randomised, multi-centre, double-masked, active-controlled study (QUASAR) in patients with treatment naïve macular oedema secondary to RVO.

The primary objective was to determine if treatment with Eylea 114.3 mg/ml at intervals of 8 weeks (8Q8) provides non-inferior best corrected visual acuity (BCVA) change compared to Eylea 40 mg/ml every 4 weeks (2Q4).
The secondary objectives included to determine if treatment with 8Q8 requires less injections compared to 2Q4, to determine the effect of Eylea 114.3 mg/ml versus Eylea 40 mg/ml on anatomic and other visual measures of response, and to evaluate the safety and pharmacokinetics of aflibercept.

The primary efficacy endpoint was the change from baseline in BCVA measured by the early treatment diabetic retinopathy study (ETDRS) letter score at week 36.

The key secondary endpoint was the number of active injections from baseline to week 64.
Further secondary endpoints were the number of active injections from baseline to week 36, the proportion of patients gaining at least 15 letters in BCVA from baseline at week 36, the proportion of patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at week 36, and the change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at week 36, among others.

In the QUASAR study a total of 892 patients were treated. The patients were assigned in a 1:1:1 ratio to 1 of 3 parallel treatment groups:
1. Eylea 114.3 mg/ml administered every 8 weeks, after 3 initial injections at 4-weeks intervals (8Q8/3)
2. Eylea 114.3 mg/ml administered every 8 weeks, after 5 initial injections at 4-weeks intervals (8Q8/5)
3. Eylea 40 mg/ml administered every 4 weeks (2Q4)

From week 16 (8Q8/3), week 24 (8Q8/5) and week 40 (2Q4, if previously extended to Q8), patients were eligible to have their dosing interval shortened by 4 weeks if both of the following criteria were met at a dosing visit:
1. >5 letter loss in BCVA from reference visit, and
2. >50 microns increase in CRT from reference visit.

Extension of interval was allowed starting from week 32 (2Q4 and 8Q8/3) or week 40 (8Q8/5) by 4 weeks increments if both of the following criteria were met at a dosing visit:
1. <5 letter loss in BCVA from reference visit, and
2. CRT <320 microns on SD-OCT (or <300 microns if excluding RPE).

Reference visits were at week 12 for 8Q8/3 and week 20 for 8Q8/5 and 2Q4.

For patients who did not meet the criteria for shortening or extension of the interval, the dosing interval was maintained. The minimum interval between injections was 4 weeks in all groups.

Patients with bilateral disease were eligible to receive Eylea 40 mg/ml treatment or another anti-VEGF medicinal product in their fellow eye.

Patient characteristics at baseline
Patients ages ranged from 23 to 95 years with a mean of 65.9 years.
Approximately 57% (168/293) and 57% (170/298) of the patients randomized to the 8Q8/3- and 8Q8/5- groups, respectively, were 65 years of age or older and approximately 26% (76/293) and 25% (74/298) were 75 years of age or older.
425 (48%) of enrolled patients had CRVO/HRVO and 467 (52%) had BRVO. The proportions of patients per subtype were similar across treatment groups.

Results
Treatment with Eylea 114.3 mg/ml was shown to be non-inferior and clinically equivalent to treatment with 2Q4 in terms of the primary efficacy endpoint ‘change from baseline in BCVA’ measured by the ETDRS letter score at week 36.

Furthermore, treatment with Eylea 114.3 mg/ml was shown to be superior to treatment with 2Q4 in terms of the key secondary efficacy endpoint ‘number of active injections from baseline to week 64’. The Eylea 8Q8/3-group required 3.2 fewer injections than the 2Q4-group.

At week 36, 93.9% of patients in the 8Q8/3-group had attained treatment intervals of ≥8 weeks, while maintaining visual and anatomic outcomes.
At week 64, 56.1% of patients in the 8Q8/3-group had completed treatment intervals of 16 weeks, while maintaining visual and anatomic outcomes.
At week 64, 40.5% of patients in the 8Q8/3-group had last intended treatment intervals of 20 weeks, while maintaining visual and anatomic outcomes.

Table 9: Efficacy outcomes from the QUASAR study

Efficacy outcomes	**Week**	**Eylea 8Q8/3 (N = 293)**	**Eylea 2Q4 (N = 301)**
Change in BCVA from baseline as measured by ETDRS letter score [A]			
Arithmetic mean (SD), observed	36	17.0 (11.8)	17.8 (13.1)
LS mean (SE) [B]		17.4 (0.7)	17.5 (0.7)
Difference in LS means (95% CI) [B, C]		-0.1 (-2.0, 1.9)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [B, C]		<0.0001	
Arithmetic mean (SD), observed	64	17.3 (12.7)	17.4 (14.6)
LS mean (SE) [B]		17.8 (0.7)	17.3 (0.8)
Difference in LS means (95% CI) [B, C]		0.5 (-1.6, 2.7)	
CRVO/HRVO [D]			
Arithmetic mean (SD), observed	36	16.5 (12.7)	16.2 (14.7)
LS mean (SE) [B]		16.6 (1.1)	15.9 (1.2)
Difference in LS means (95% CI) [B, C]		0.6 (-2.6, 3.9)	
Arithmetic mean (SD), observed	64	16.5 (13.8)	14.8 (16.8)
LS mean (SE) [B]		17.2 (1.2)	15.2 (1.3)
Difference in LS means (95% CI) [B, C]		2.0 (-1.5, 5.6)	
BRVO [D]			
Arithmetic mean (SD), observed	36	17.4 (10.9)	19.4 (11.0)
LS mean (SE) [B]		18.3 (0.8)	19.0 (0.8)
Difference in LS means (95% CI) [B, C]		-0.8 (-2.9, 1.4)	
Arithmetic mean (SD), observed	64	18.1 (11.8)	20.1 (11.4)
LS mean (SE) [B]		18.4 (0.9)	19.6 (0.8)
Difference in LS means (95% CI) [B, C]		-1.1 (-3.5, 1.2)	
Patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) [A]			
Proportion (OC)	36	72.7%	67.8%
	64	70.4%	70.2%
Patients who gained at least 15 letters in BCVA from baseline [A]			
Proportion (OC)	36	58.8%	59.8%
	64	61.7%	60.4%
Patients who lost at least 15 letters in BCVA from baseline [A]			
Proportion (OC)	36	1.2%	1.5%
	64	1.2%	2.4%
Patients with no IRF and no SRF in the central subfield [A]			
Proportion (OC)	36	81.2%	83.7%
	64	76.3%	66.0%
Number of active injections			
Arithmetic mean (SD), observed [E]	36	6.1 (0.6)	8.8 (0.8)
LS mean (SE) [F]		6.1 (0.0)	8.8 (0.0)
Difference in LS means (95% CI) [F, C]		-2.7 (-2.8, -2.6)	
Arithmetic mean (SD), observed [E]	64	8.4 (1.2)	11.7 (1.6)
LS mean (SE) [F]		8.5 (0.1)	11.7 (0.1)
Difference in LS means (95% CI) [F, C]		-3.2 (-3.5, -3.0)	
p-value (two-sided superiority test) [G, C]		<0.0001	
Maintenance of treatment intervals			
Patients maintained with ≥Q8 treatment interval [E]			
Proportion	36	88.5%	n/a
	64	88.1%	70.0% [H]

Efficacy outcomes	Week	Eylea 8Q8/3 (N = 293)	Eylea 2Q4 (N = 301)
Last completed treatment intervals			
Patients at Q4 treatment interval [E]			
Proportion	64	4.8%	13.0%
Patients at ≥Q8 treatment interval [E]			
Proportion	64	95.2%	87.0%
Patients at ≥Q12 treatment interval [E]			
Proportion	64	81.4%	67.8%
Patients at Q16 treatment interval [E]			
Proportion	64	56.1%	n/a
Last intended treatment intervals			
Patients at ≥Q8 treatment interval [E]			
Proportion	36	93.9%	75.6%
	64	95.9%	92.2%
Patients at Q12 treatment interval [E]			
Proportion	36	69.1%	n/a
	64	21.9%	27.8%
Patients at ≥Q12 treatment interval [E]			
Proportion	64	86.2%	77.8%
Patients at ≥Q16 treatment interval [E]			
Proportion	64	64.3%	50.0%
Patients at Q20 treatment interval [E]			
Proportion	64	40.5%	n/a

[A] Full analysis set

[B] LS mean, CI and p-value based on an MMRM with baseline best corrected visual acuity (BCVA) measurement as covariate, treatment group as factor, visit and stratification variables used for randomisation (geographical region, categorical baseline BCVA and RVO type) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.

[C] Absolute difference is Eylea 8Q8/3-group minus 2Q4-group.

[D] The number of patients with CRVO/HRVO was 134 and 152 in the 8Q8/3- and 2Q4-treatement groups, respectively. The number of patients with BRVO was 159 and 149 in the 8Q8/3- and 2Q4-treatement groups, respectively.

[E] Safety analysis set; patients considered as completer for the respective timepoint

[F] LS mean and CI based on a multiple imputation procedure applying a linear regression model adjusted for baseline BCVA, baseline central subfield thickness (CST), and the stratification variables used for randomisation (geographical region, categorical baseline BCVA and RVO type) on each imputed dataset and combination of results using Rubin`s rule.

[G] p-value based on a multiple imputation procedure applying a non-parametric rank analysis of covariance adjusted for baseline BCVA, baseline CST, and the stratification variables used for randomisation (geographical region, categorical baseline BCVA and RVO type) on each imputed dataset and combination of results using Rubin`s rule.

[H] patients in the 2Q4-treatement group who extended at week 32 and were maintained at ≥Q8 through week 64.

CI: Confidence interval

ETDRS: early treatment diabetic retinopathy study

OC: observed cases, data after the occurrence of an intercurrent event excluded in line with the primary estimand strategy

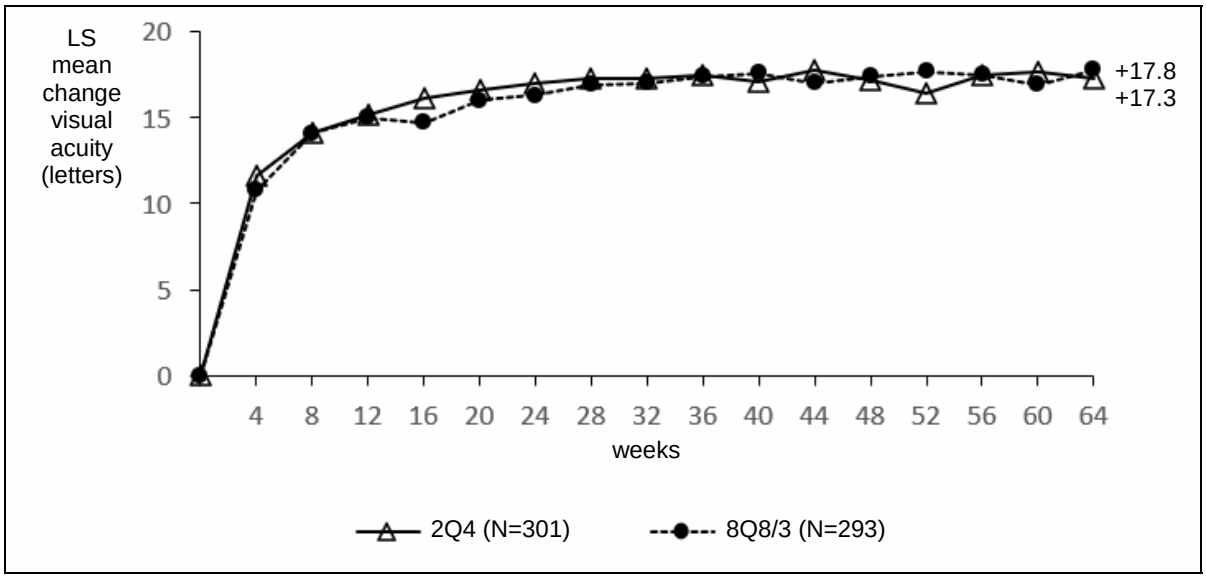
LS: Least square

MMRM: mixed model for repeated measurements

SD: Standard deviation

SE: Standard error

Figure 8: LS mean change in BCVA as measured by ETDRS letter score from baseline through week 64 (full analysis set) in the QUASAR study



Eylea at all doses (8Q8/3, 2Q4) showed meaningful increase from baseline in the pre-specified secondary efficacy endpoint national eye institute visual function questionnaire (NEI VFQ-25). The magnitude of these changes was in line to that seen in published studies, reflected by improvements in visual related quality of life.

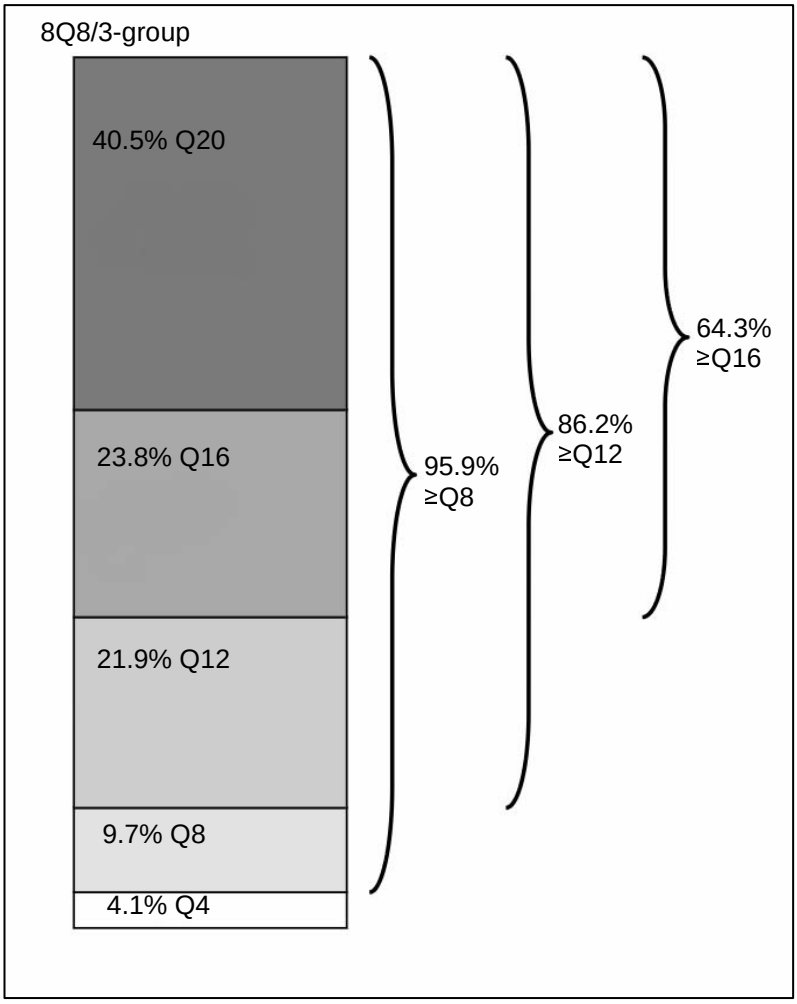
No clinically meaningful differences were found between the 8Q8/3-, and 2Q4-groups in changes of NEI VFQ-25 total score at week 36 and week 64 from baseline.

Efficacy results in pre-specified evaluable subgroups for RVO sub-types, age, gender, geographic region, ethnicity, race, baseline BCVA and baseline CRT were consistent with the results in the overall population.

Efficacy was generally maintained through week 64.

On the pre-specified secondary endpoint ‘participants dosed only 8Q8 through week 36 in the Eylea 114.3 mg/ml 8Q8 group’, 88.5% of patients in the 8Q8/3-group were maintained on their original randomisation treatment interval of 8 weeks, while maintaining visual and anatomic outcomes.

Figure 9: Last intended treatment intervals at week 64



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with aflibercept in all subsets of the paediatric population in nAMD, DMO and RVO (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption / Distribution

Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive, stable complex with VEGF; however only “free aflibercept” is able to bind endogenous VEGF.

Following unilateral intravitreal administration of 8 mg aflibercept, the mean (SD) C_{max} of free aflibercept in plasma was 0.25 (0.21) mg/l, and the median time to maximal concentration in plasma was 1 day, in the nAMD and DMO population combined. The accumulation of free aflibercept in plasma following 3 initial monthly doses was minimal. Subsequently, no further accumulation was observed. These data are also supported by population pharmacokinetic analyses.

These pharmacokinetic results were consistent with data obtained in patients with RVO.

Elimination

Aflibercept is a protein-based therapeutic and no metabolism studies have been conducted.

Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The median time to reach the last quantifiable concentration of free aflibercept in plasma for 8 mg administered intravitreally was 3 weeks.

Renal or hepatic impairment

No special studies in patients with renal or hepatic impairment have been conducted with Eylea 114.3 mg/ml.

The systemic exposures to aflibercept in patients with mild to severe renal impairment were similar to those with normal renal function. Limited available data in patients with mild hepatic impairment do not indicate an influence on systemic exposures to aflibercept compared to patients with normal hepatic function.

5.3 Preclinical safety data

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at systemic exposures in excess of the maximum human exposure. The systemic exposure for free aflibercept was approximately 26- and 33-fold higher based on C_{max} and AUC when compared to corresponding values in adult patients after an intravitreal dose of 8 mg. At the No Observed Adverse Effect Level (NOAEL) of 0.5 mg/eye in monkeys the systemic exposure was 3.2- and 3.8-fold higher based on C_{max} and AUC when compared to corresponding values in adult patients.

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept.

An effect of aflibercept on intrauterine development was shown in embryo-foetal development studies in pregnant rabbits with intravenous (3 to 60 mg/kg) as well as subcutaneous (0.1 to 1 mg/kg) administration. The maternal NOAEL was at the dose of 3 mg/kg or 1 mg/kg, respectively. A developmental NOAEL was not identified. At

the 0.1 mg/kg dose, the systemic exposure for free aflibercept was approximately 1.0- and 1.0-fold based on C_{max} and cumulative AUC when compared to corresponding values in adult patients after an intravitreal dose of 8 mg.

Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. Based on C_{max} and AUC for free aflibercept observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 377-fold and 104-fold higher, respectively, than the exposure in humans after an intravitreal dose of 8 mg. All changes were reversible.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

Arginine hydrochloride

Histidine hydrochloride monohydrate

Histidine

Polysorbate 20

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the pre-filled syringe in its blister and in the outer carton in order to protect from light.

Prior to usage, the unopened blister may be stored outside the refrigerator below 25 °C for up to 24 hours.

6.5 Nature and contents of container

Pre-filled syringe (type I glass) with a grey plunger stopper (elastomeric rubber), a white Luer-lock adaptor with a grey tip cap (elastomeric rubber) and a blue OcuClick dosing system (PC/ABS plastic).

Each pre-filled syringe contains 0.184 ml solution.

Pack size of 1 pre-filled syringe.

6.6 Special precautions for disposal

The pre-filled syringe with OcuClick dosing system is for single use in one eye only. Extraction of multiple doses from a single pre-filled syringe with OcuClick dosing system may increase the risk of contamination and subsequent infection.

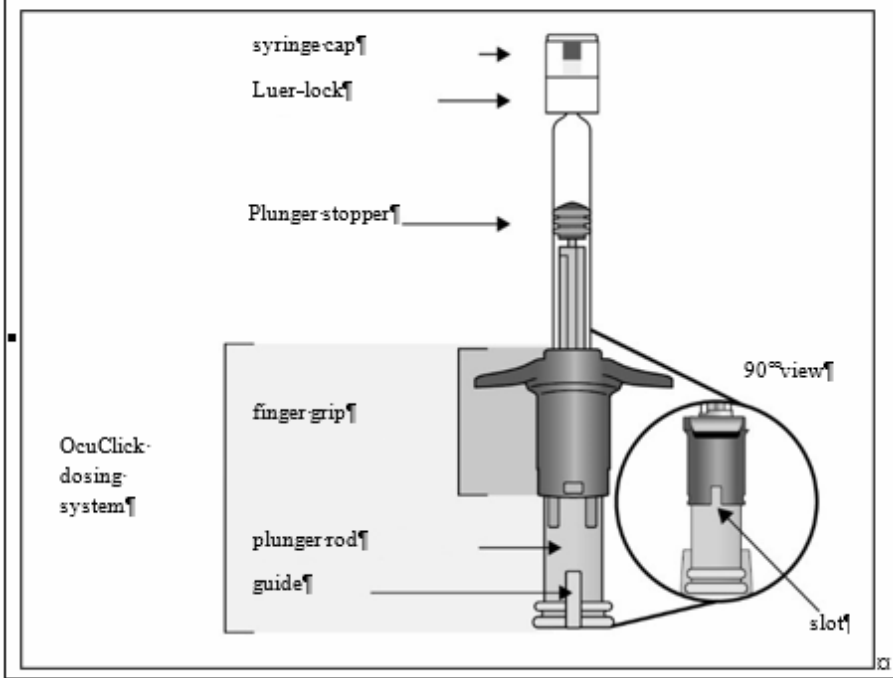
Do not use if the package or its components are expired, damaged, or have been tampered with.

Check the label on the pre-filled syringe with OcuClick dosing system to make sure you have the strength of Eylea that you intended to use. The 8 mg dose requires use of the Eylea 114.3 mg/ml pre-filled syringe.

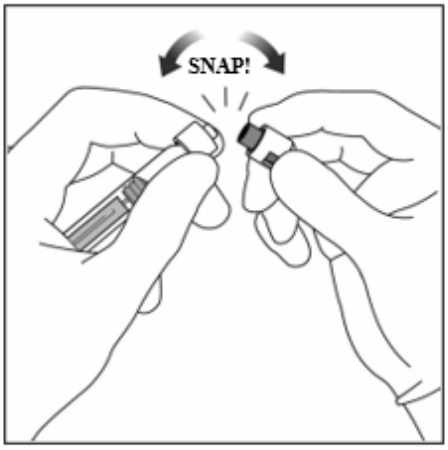
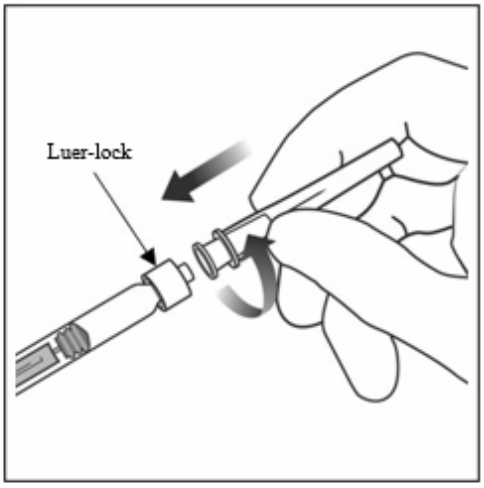
The intravitreal injection should be performed with a 30 G × ½ inch injection needle (not included).

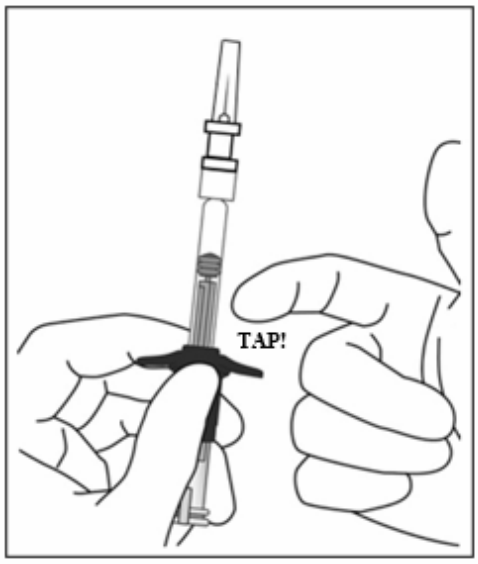
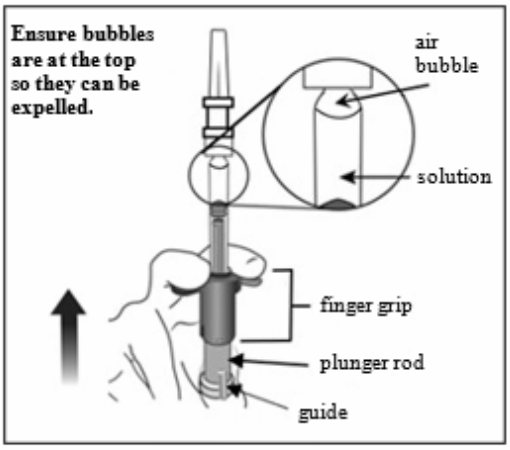
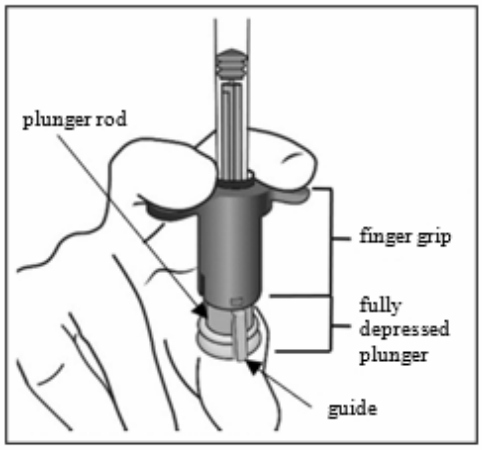
Use of a smaller size needle (higher gauge) than the recommended 30 G × ½ inch injection needle may result in increased injection forces.

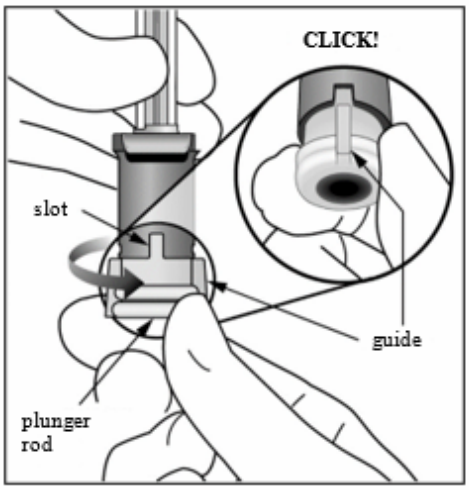
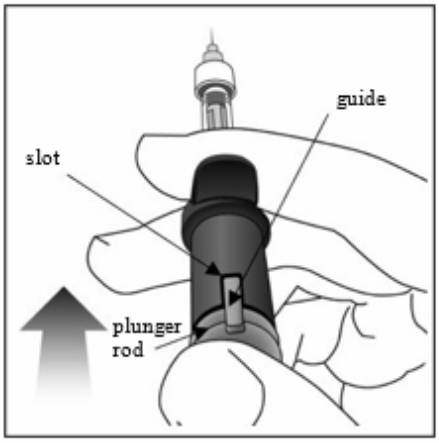
Pre-filled syringe with integrated OcuClick dosing system description



1.	Prepare When ready to administer Eylea® 114.3 mg/ml, open the carton and remove the sterile blister. Carefully peel open the blister ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready to attach the injection needle. Use aseptic technique to carry out steps 2-9.
2.	Remove syringe Remove the syringe from the sterilised blister.
3.	Inspect syringe and solution for injection **Do not** use the pre-filled syringe if - → particulates, cloudiness, or discolouration are visible - → any part of the pre-filled syringe with OcuClick dosing system is damaged or loose

	- the syringe cap is detached from the Luer-lock.
4.	Snap off syringe cap To **snap off** (do not twist off) the syringe cap, hold the syringe in one hand and the syringe cap with the thumb and forefinger of the other hand. **Note:** Do not pull back on the plunger rod. 
5.	Attach needle Firmly twist the 30 G × ½ inch injection needle onto the Luer-lock syringe tip. 
6.	Dislodge air bubbles

	Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.	
7.	Expel air and excess volume to prime The syringe does not have a dose line because it is designed to set the dose mechanically as explained in the steps below. Priming and setting the dose must be done using the following steps. To eliminate all bubbles and to expel excess medicinal product, slowly depress the plunger rod (left picture below) until it stops, i.e. when the guide on the plunger rod reaches the finger grip (right picture below).  
8.	Set the dose	

	Turn the end of the plunger rod 90 degrees clockwise or counter clockwise until the guide of the plunger rod aligns with the slot. You may hear a 'click'. **Note:** Now the device is ready to dose. Do not push the plunger rod before insertion into the eye.	
9.	Administer the injection Insert the needle into the ocular injection site. Inject the solution by pushing in the plunger rod until it stops, i.e. until the guide is completely within the slot. Do not apply additional pressure once the guide is within the slot. It is normal to see a small amount of residual solution left in the syringe.	
10.	The pre-filled syringe is for single dose administration and single use only. After injection discard the used syringe into a sharps container.	

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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