Full title of trial	Prospective non-randomised exploratory study to assess the safety and efficacy of Eylea in cystoid macular oedema associated with Retinitis Pigmentosa
Short title	Aflibercept for Macular Oedema with Underlying Retinitis Pigmentosa (AMOUR) study
Version and date of protocol	Version 2.0 26th November2015
Sponsor:	Moorfields Eye Hospital NHS Foundation Trust
Sponsor protocol number	MICM1014
Funder (s) :	Bayer PLC
EudraCT no	2015-003723-65
ACTIVE IMP(s):	Aflibercept (Eylea)
PLACEBO IMP(s):	N/A
Phase of trial	Therapeutic exploratory trial (phase II)
Sites(s)	Single site – Moorfields Eye Hospital

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Signatures

The Chief Investigator and the R&D (sponsor office) have discussed this protocol.

The investigators agree to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Michel Michaelides

Signature Date

Sponsor Representative

Gisela Barreto

Moorfields Eye Hospital Signature Date

Contents

List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CMO	Cystoid Macular Oedema
CMT	Central Macular Thickness
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File

ISRCTN	International Standard Randomised
IVT	Intravitreal injection
MA	Marketing Authorisation
MEH	Moorfields Eye Hospital
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
OCT	Optical Coherence Tomography
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
RP	Retinitis Pigmentosa
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

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2 Summary

Full title	Prospective non-randomised exploratory study to assess the safety and efficacy of Eylea in cystoid macular oedema associated with Retinitis Pigmentosa
Short title	Aflibercept for Macular Oedema with Underlying Retinitis Pigmentosa (AMOUR)
Trial medication:	Aflibercept (Eylea)
Phase of trial:	Therapeutic exploratory trial (phase II)
Objectives:	To assess the safety and efficacy of Eylea in cystoid macular oedema (CMO) associated with Retinitis Pigmentosa (RP)Primary End-point: ➢ Mean Central Macular Thickness (CMT) on Spectral Domain OCT (SDOCT) at 12 months Secondary End-points: ➢ Mean Central Macular Thickness (CMT) on Spectral Domain OCT (SDOCT) at 6 months ➢ Mean change in CMT on SDOCT from baseline to

6 months and baseline to 12 months

- Mean Best Corrected ETDRS Visual Acuity (BCVA) at 6 and 12 months
- Mean change in ETDRS BCVA from baseline to 6 months and baseline to 12 months
- Mean macular volume on SDOCT at 6 and 12 months
- Mean change in macular volume on SDOCT from baseline to 6 months and baseline to 12 months
- Report all AEs and SAEs
- Mean retinal sensitivity using microperimetry at 6 and 12 months
- Mean change in retinal sensitivity using microperimetry from baseline to 6 months and baseline to 12 months
- Mean number of intravitreal injections administered

Type of trial: Therapeutic exploratory trial (phase II), prospective, non-randomised, single site exploratory trial in patients with Retinitis Pigmentosa associated with cystoid macula oedema

Trial design and methods:

- 16 years of age, Prospective, non-randomised, Molecularly confirmed patients prioritised (to be able to potentially explore any pharmacogenetic aspects), Recruited over a 9 month period, with each patient having 12 month follow-up.
- All patients receive 3 loading injections of Eylea at monthly intervals followed by a treat and extend

protocol up to 12 months, Extension from monthly to 6, 8, 10 and 12 week follow-up will occur when there is evidence of OCT stability in the view of the investigator i.e. there is no further reduction in macular fluid compared to the previous visit.

- All patients will receive 5 injections before considering them non-responders
- BCVA and SDOCT undertaken at every visit
- Microperimetry undertaken at Baseline, 6 months and 12 months
- Fundus Autofluorescence (FAF) Imaging Baseline, 6 and 12 months
- Refracted BCVA at baseline, 6 months and 12 months
- SDOCTs will be graded by Moorfields Eye Hospital Reading Centre

Trial duration per participant:	12 months
Estimated total trial duration:	24 months
Planned trial sites:	Single-site
Total number of participants planned:	30

inclusion/exclusion criteria:

Inclusion criteria:

- CMO in association with RP
- 16 years of age
- Unilateral or Bilateral CMO (the worse eye only will be treated – defined as the eye with a greater central macular thickness (CMT) on OCT)
- No previous oral treatment for CMO for last 3 months
- No previous peribulbar or intravitreal treatment for CMO in the study eye for last 3 months
- No previous topical treatment for CMO in the study eye for last 1 month
- Central visual impairment that in the view of the Principal Investigator is due to CMO
- BCVA better than 3/60

Exclusion criteria:

- Insufficient patient cooperation or media clarity to allow adequate fundus imaging
- Evidence of visually significant vitreo-retinal traction or epiretinal membrane on OCT that in the Principal Investigator's opinion is highly likely to significantly limit the efficacy of intravitreal therapy
- History of cataract surgery within prior 3 months or cataract surgery anticipated within 6 months of starting the study
- Any anti-VEGF treatment to study eye within 3 months
- History of YAG capsulotomy performed within 3

months

- Uncontrolled IOP > = 24 mmHg for ocular hypertension (on topical IOP lowering medications)
- Advanced glaucoma (in the opinion of a glaucoma specialist)
- Patients with active or suspected ocular or periocular infections
- Patients with active severe intraocular inflammation
- Patients with a new, untreated retinal tear or detachment
- Patients with a stage 3 or 4 macular hole
- Thromboembolic event (MI/CVA/Unstable Angina) within 6 months
- Pregnancy or family planned within 15 months
- Females who are breast feeding
- Known allergy or hypersensitivity to anti-VEGF products

Statistical methodology and analysis:

A consort flow chart will be constructed to illustrate the flow of patients through the study. The primary analysis will be an available case analysis but baseline characteristics of those who are lost to follow up will be compared with those who are not. If the findings from this study are favourable, these data will be used to plan a definitive randomised controlled trial. A third of patients showing more than 40% reduction in CMT on OCT would be 'favourable' and supportive of further study

3 Introduction

3.1 Background

- Inherited retinal disease is the second commonest cause of visual loss in childhood and the commonest cause of visual loss in the working age population
- Retinitis Pigmentosa (RP) is the commonest inherited retinal disorder with an incidence of 1 in 3,000
- There are no cures currently for RP
- Patients with RP experience two complications for which there is potential treatment – cataracts and cystoid macular oedema (CMO)
- Approximately 20% of patients with RP develop CMO which causes significant central visual loss and disability
- Several different treatments for CMO have been employed including laser therapy, topical trusopt, oral acetazolamide, peri-ocular and intravitreal steroids, and intravitreal anti-VEGF agents
- The current mainstay of treatment are topical and oral carbonic anhydrase inhibitors
- The vast majority of the published literature is retrospective and thereby inherently limited and often involves small numbers of participants and short duration of follow-up

3.2 Preclinical data

- In a retrospective review of patients seen at Moorfields Eye Hospital in the Retinal Genetics Clinics (Professors Moore, Michaelides and Webster) with RP on treatment for CMO (n=93), ascertained over a 12 month period (June 2012 to June 2013), – approximately 50% were deemed non-responders (defined as less than 20% reduction in central macular thickness (CMT) on OCT between visits) to topical or systemic carbonic anhydrase inhibitors

3.3 Clinical data

- There is some evidence in the literature that anti-VEGF therapy may be effective – Artunay *et al* (*2009*) observed significant response to a single injection of Lucentis in 15 eyes of 15 patients with RP and CMO over a 6 month follow-up period

3.4 Rationale and risks/benefits

Primary research question:

1) Is there a reduction in central macular thickness (CMT) in patients with Retinitis Pigmentosa associated with cystoid macula oedema after the use of Eylea?

Treatment currently available and their limitations:

- Includes: laser therapy, topical trusopt, oral acetazolamide, peri-ocular and intravitreal steroids, and intravitreal anti-VEGF agents. The current mainstay of treatment are topical and oral carbonic anhydrase inhibitors
- The vast majority of the published literature is retrospective and thereby inherently limited and often involves small numbers of participants and short duration of follow-up
- In a retrospective review of patients seen at Moorfields Eye Hospital in the Retinal Genetics Clinics (Professors Moore and Webster, and Mr Michaelides) with RP on treatment for CMO (n=93), ascertained over a 12 month period (June 2012 to June 2013), – approximately 50% were deemed non-responders (defined as less than 20% reduction in CMT on OCT between visits) to topical or systemic carbonic anhydrase inhibitors

- There is some evidence in the literature that anti-VEGF therapy may be effective – Artunay *et al* (*2009*) observed significant response to a single injection of Lucentis in 15 eyes of 15 patients with RP and CMO over a 6 month follow-up period
- A case report by Moustafa G.A and Moschos M (2015) observed improvement in BCVA and reduction of macula oedema following treatment with a single injection of Eylea in a patient with RP associated CMO
- Professor Michel Michaelides has observed similar responses in two patients treated with Eylea who had failed all other treatments

Risk/benefit analysis of Eylea

Risks

Intravitreal injection-related reactions

Intravitreal injections, including those with Eylea, have been associated with endophthalmitis (1 in 2000), intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. 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.

Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea. Special precaution is needed in patients with poorly controlled glaucoma (Eylea must not be injected if the intraocular pressure is ≥ 30 mmHg). In all cases, both the intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately if it is thought to be compromised in any way.

Immunogenicity

Being a therapeutic protein, there is a potential for immunogenicity with Eylea. 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. There are limited data on safety in the treatment of patients with CRVO, BRVO or DMO with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients

Other

As with other intravitreal anti-VEGF treatments for AMD, CRVO, BRVO and DMO the following also applies:

• The safety and efficacy of Eylea therapy administered to both eyes concurrently has not been systematically studied. 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.

• There is no data available on the concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular).

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

• Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.

• In the event of a retinal break the dose should be withheld and treatment should not be resumed until the break is adequately repaired.

• The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:

• a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity;

• a sub-retinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area.

• The dose should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery.

• Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus.

• Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept.

Populations with limited data

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.

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Adjunctive use of verteporfin photodynamic therapy (PDT) and Eylea has not been studied, therefore, a safety profile is not established.

Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept.

Pregnancy

There are no data on the use of aflibercept in pregnant women. Studies in animals have shown embryo-foetal toxicity. Although the systemic exposure after ocular administration is very low, Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Breastfeeding

It is unknown whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded. Eylea is therefore not recommended during breastfeeding. A decision must be made whether to discontinue breastfeeding or to abstain from Eylea therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility. Such effects are not expected after ocular administration with very low systemic exposure.

4.7 Effects on ability to drive and use machines

Injection with Eylea has a minor influence on the ability to drive and use machines due to possible temporary visual disturbances associated either with the injection or the 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

The following information has been taken from the electronic Medicines Compendium (eMC): https://www.medicines.org.uk/emc/medicine/27224.
A total of 2,957 patients constituted the safety population in the seven phase III studies. Among those, 2,356 patients were treated with the recommended dose of 2 mg.

Serious adverse reactions related to the injection procedure have occurred in less than 1 in 2,200 intravitreal injections with Eylea and included blindness, endophthalmitis, retinal detachment, cataract traumatic, vitreous haemorrhage, cataract, vitreous detachment, and intraocular pressure increased (see section 4.4). The most frequently observed adverse reactions (in at least 5% of patients treated with Eylea) were conjunctival haemorrhage (24.9%), visual acuity reduced (10.7%), eye pain (9.9%), intraocular pressure increased (7.1%), vitreous detachment (6.8%), vitreous floaters (6.6%) and cataract (6.6%).

Tabulated list of adverse reactions

The safety data described below include all adverse reactions from the seven phase III studies in the indications wet AMD, CRVO, BRVO and DMO with a reasonable possibility of causality to the injection procedure or medicinal product.

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). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 1: All treatment-emergent adverse drug reactions reported in patients in phase III studies (pooled data of the phase III studies for the indications wet AMD, CRVO, BRVO and DME). (Bayer plc., 2015)

System Organ Class	Very common	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity***	
Eye disorders	Visual acuity reduced, Conjunctival haemorrhage,	Retinal pigment epithelial tear*, Detachment of the retinal pigment epithelium, Retinal degeneration, Vitreous haemorrhage, Cataract, Cataract nuclear, Cataract subcapsular, Cataract cortical, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Corneal oedema, Vitreous detachment, Injection site pain, Eye pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia, Ocular hyperaemia	Blindness, Endophthalmitis**, Retinal detachment, Retinal tear, Iritis, Uveitis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Injection site irritation, Abnormal sensation in eye, Eyelid irritation, Anterior chamber flare	Cataract traumatic, Vitritis Hypopyon

* Conditions known to be associated with wet AMD. Observed in the wet AMD studies only.
** Culture positive and culture negative endophthalmitis
*** including allergic reactions

Description of selected adverse reactions

In the wet AMD phase III studies, there was an increased incidence of conjunctival haemorrhage in patients receiving anti-thrombotic agents. This increased incidence was comparable between patients treated with ranibizumab and Eylea.

Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

ATEs, as defined by Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause).

The incidence of ATEs in the phase III wet AMD studies during the 96 weeks study duration was 3.3% (60 out of 1,824) in the combined group of patients treated with Eylea compared to 3.2% (19 out of 595) in patients treated with ranibizumab (see section 5.1). The corresponding numbers in the DME studies during the first 52 weeks were 3.3% (19 out of 578) (Eylea) and 2.8% (8 out of 287) (control group) (see section 5.1).

The incidence of ATEs in the phase III CRVO studies during the 76/100 weeks study duration was 0.6% (2 out of 317) in patients treated with at least one dose of Eylea compared to 1.4% (2 out of 142) in the group of patients receiving only sham treatment (see section 5.1) whilst for the Phase III BRVO study during the 52 weeks study duration it was 0% (0 out of 91) in patients treated with Eylea compared with 2.2% (2 out of 92) in the control group (see section 5.1). One of these patients in the control group had received Eylea rescue treatment.

As with all therapeutic proteins, there is a potential for immunogenicity with Eylea.

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.

Overdose

In clinical trials doses of up to 4 mg in monthly intervals have been used and isolated cases of overdoses with 8 mg occurred.

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.

Benefits

Eylea has been shown to improve visual acuity and reduce central macular thickness in wet AMD, as well as oedema secondary to CRVO, BRVO and DMO. Please see below for the literature surrounding this. It is hoped that Eylea will achieve similar effects for patients who have oedema associated with RP.

Pharmacodynamic effects

Wet AMD

Wet AMD is characterised by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid from CNV may cause retinal thickening or oedema and/or sub-/intra-retinal haemorrhage, resulting in loss of visual acuity. In patients treated with Eylea (one injection per month for three consecutive months, followed by one injection every 2 months), retinal thickness decreased soon after treatment initiation, and the mean CNV lesion size was reduced, consistent with the results seen with ranibizumab 0.5 mg every month.

In the VIEW1 study there were mean decreases in retinal thickness on optical coherence tomography (OCT) (-130 and -129 microns at week 52 for the Eylea 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively). Also at the 52 week time point, in the VIEW2 study there were mean decreases in retinal thickness on OCT (-149 and -139 microns for the Eylea 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively).
The reduction of CNV size and reduction in retinal thickness were generally maintained in the second year of the studies.

Macular Oedema secondary to CRVO and BRVO

In CRVO and BRVO 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.

In patients treated with Eylea (one injection every month for six months) there was consistent, rapid and robust response in morphology (central retinal thickness [CRT] as assessed by OCT). Improvements in mean CRT were maintained through week 24.

Retinal thickness on OCT at week 24 compared to baseline was a secondary efficacy variable in the COPERNICUS and GALILEO studies (CRVO) and the

VIBRANT study (BRVO). In all three studies, the mean change in CRT from baseline to week 24 was statistically significant, favouring Eylea.

In the COPERNICUS and GALILEO studies the mean decrease from baseline in retinal thickness on OCT at week 24 was significantly greater in patients treated with Eylea 2 mg every month than in the control group (-457 microns vs. -145 microns in COPERNICUS, and -449 microns vs. -169 microns in GALILEO). The decrease from baseline in retinal thickness was maintained to the end of study, week 100 in COPERNICUS, and to week 76 in GALILEO.

In the VIBRANT study the mean decrease from baseline in retinal thickness on OCT at week 24 was significantly greater in patients treated with Eylea 2 mg every month than in the control group (-280 microns vs. -128 microns). This decrease from baseline was maintained to week 52.

Diabetic macular oedema

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

In patients treated with Eylea, rapid and robust response in morphology (central retinal thickness [CRT]) as assessed by OCT was seen soon after treatment initiation. The mean change in CRT from baseline to week 52 was statistically significant favoring Eylea.

In the VIVID-DME study there were mean decreases in retinal thickness on optical coherence tomography (OCT) (-192.4 and -66.2 microns at week 52 for the Eylea 2Q8 and laser group, respectively). Also at the 52 week time point, in the VISTA-DME study there were mean decreases in retinal thickness on OCT (-183.1 and -73.3 microns for the Eylea 2Q8 and laser group, respectively).

<u>Clinical efficacy and safety</u>

Wet AMD

The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with wet AMD. A total of 2,412 patients were treated and evaluable for efficacy (1,817 with Eylea) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

1) Eylea administered at 2 mg every 8 weeks following 3 initial monthly doses (Eylea 2Q8);
2) Eylea administered at 2 mg every 4 weeks (Eylea 2Q4);
3) Eylea administered at 0.5 mg every 4 weeks (Eylea 0.5Q4); and
4) ranibizumab administered at 0.5 mg every 4 weeks (ranibizumab 0.5Q4).

Patient ages ranged from 49 to 99 years with a mean of 76 years.
In the second year of the studies, patients continued to receive the dosage strength to which they were initially randomised but on a modified dosing schedule guided by assessment of visual and anatomic outcomes with a protocol-defined maximum dosing interval of 12 weeks.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline.

In the VIEW1 study, at week 52, 95.1% of patients in the Eylea 2Q8 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. Eylea treatment was shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

In the VIEW2 study, at week 52, 95.6% of patients in the Eylea 2Q8 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group.

Eylea treatment was shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

Detailed results from the combined analysis of both studies are shown in the Table 2 and Figure 1 below.

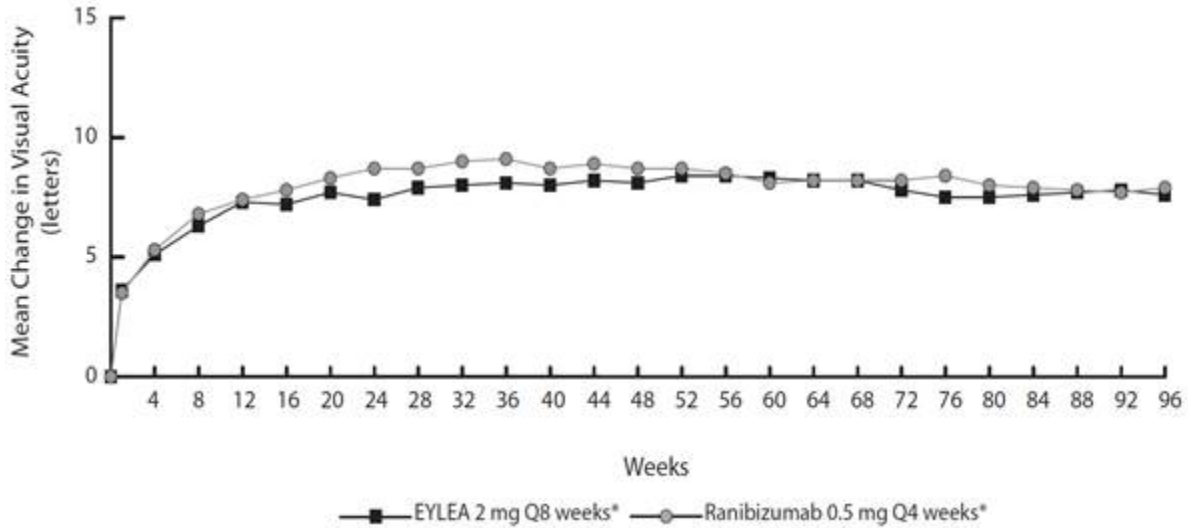
Table 2: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW1 and VIEW2 studies[B)] (Bayer plc., 2015)

Efficacy Outcome	**Eylea 2Q8** [E)] (Eylea 2 mg every 8 weeks following 3 initial monthly doses) **(N = 607)**		**Ranibizumab 0.5Q4** (ranibizumab 0.5 mg every 4 weeks) **(N = 595)**	
	Week 52	Week 96 [G)]	Week 52	Week 96 [G)]
Mean number of injections from baseline	7.6	11.2	12.3	16.5
Mean number of injections during second year (Week 52 to 96)		4.2		4.7
Proportion of patients with maintained visual acuity (< 15 letters of BCVA[A)] loss) (Per Protocol Set)	95.33%[B)]	92.42%	94.42% [B)]	91.60%
Difference[C)] (95% CI)[D)]	0.9% (-1.7, 3.5)[F)]	0.8% (-2.3, 3.8)[F)]		
Mean change in BCVA as measured by ETDRS[A)] letter score from baseline	8.40	7.62	8.74	7.89
Difference in LS [A)] mean change (ETDRS letters)[C)] (95% CI)[D)]	-0.32 (-1.87, 1.23)	-0.25 (-1.98, 1.49)		
Proportion of patients who gained at least 15 letters of vision from baseline	30.97%	33.44%	32.44%	31.60%
Difference[C)] (95% CI)[D)]	-1.5% (-6.8, 3.8)	1.8% (-3.5, 7.1)		

[A)] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LS: Least square means derived from ANCOVA

[B)] Full Analysis Set (FAS), Last Observation Carried Forward (LOCF) for all analyses except proportion of patients with maintained visual acuity at week 52 which is Per Protocol Set (PPS)
[C)] The difference is the value of the Eylea group minus the value of the ranibizumab group. A positive value favours Eylea.
[D)] Confidence interval (CI) calculated by normal approximation
[E)] After treatment initiation with three monthly doses
[F)] A confidence interval lying entirely above -10% indicates a non-inferiority of Eylea to ranibizumab
[G)] Beginning at week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria

Figure 1. Mean Change in Visual Acuity from Baseline to Week 96 for the Combined Data from the View1 and View2 Studies



*) From Baseline to Week 52, Eylea was dosed every 8 weeks following 3 initial monthly doses. From Baseline to Week 52, ranibizumab 0.5 mg was dosed every 4 weeks. Beginning at Week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria.

The proportion of patients at week 96 gaining at least 15 letters from baseline was 33.44% in the Eylea 2Q8 group, and 31.60% in the ranibizumab 0.5Q4 group.

In combined data analysis of the VIEW1 and VIEW2 studies Eylea demonstrated clinically meaningful changes from baseline in pre-specified secondary efficacy endpoint National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in Best Corrected Visual Acuity (BCVA).

No clinically meaningful differences were found between Eylea and the reference product ranibizumab in changes of NEI VFQ-25 total score and subscales (near activities, distance activities, and vision-specific dependency) at week 52 from baseline.

Decreases in mean CNV area were evident in all dose groups in both studies.

Efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, lesion type, lesion size) in each study and in the combined analysis were consistent with the results in the overall populations.

In the second year of the studies, efficacy was generally maintained through the last assessment at week 96.

In the second year of the studies, 2-4% of patients required all injections on a monthly basis, and a third of patients required at least one injection with a treatment interval of only one month.

Elderly Population

In the clinical studies, approximately 89% (1,616/1,817) of the patients randomised to treatment with Eylea were 65 years of age or older and approximately 63% (1,139/1,817) were 75 years of age or older.

Macular Oedema secondary to CRVO

The safety and efficacy of Eylea were assessed in two randomised, multi-centre, double-masked, sham-controlled studies in patients with macular oedema secondary to CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with Eylea) in the two studies COPERNICUS and GALILEO. In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg Eylea administered every 4

weeks (2Q4) or the control group receiving sham injections every 4 weeks for a total of 6 injections.

After 6 monthly injections, patients received treatment only if they met pre-specified retreatment criteria, except for patients in the control group in the GALILEO study who continued to receive sham (control to control) until week 52. Starting from this timepoint all patients were offered treatment if they met pre-specified criteria.

Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.

Change in visual acuity at week 24 compared to baseline was a secondary efficacy variable in both COPERNICUS and GALILEO studies.

The difference between treatment groups was statistically significant in favour of Eylea in both studies. In both pivotal studies the maximal improvement in visual acuity has been achieved at month 3 with subsequent stabilisation of the effect on visual acuity and central retinal thickness until month 6. The statistically significant difference was maintained through week 52.

Detailed results from the analysis of both studies are shown in the Table 3 and Figure 2 below.

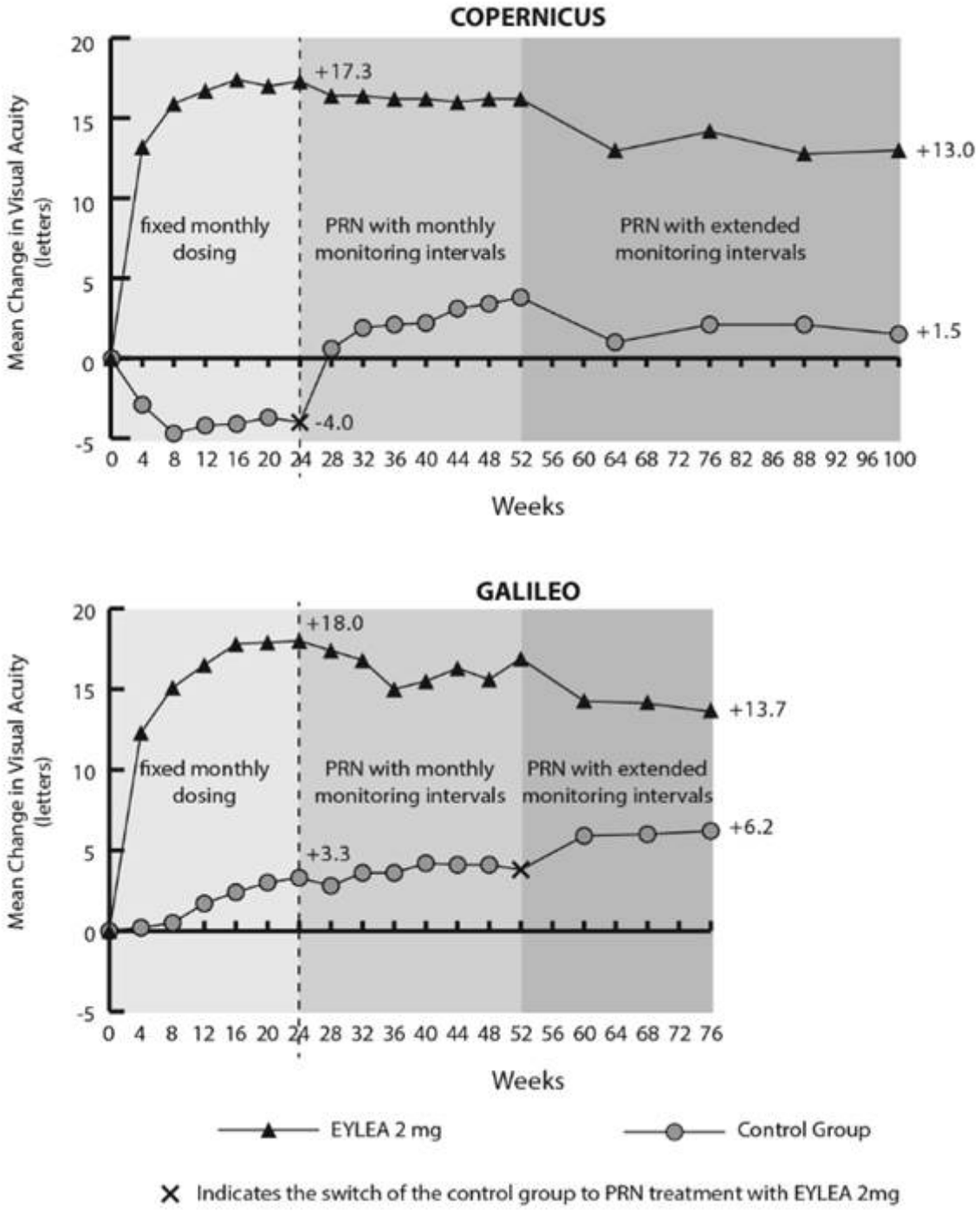
Table 3: Efficacy outcomes at week 24, week 52 and week 76/100 (Full Analysis Set with LOCF[C)]) in COPERNICUS and GALILEO studies (Bayer plc., 2015)

Efficacy Outcomes	COPERNICUS						GALILEO					
	24 Weeks		52 Weeks		100 Weeks		24 Weeks		52 Weeks		76 Weeks	
	Eylea 2 mg Q4 (N = 114)	Control (N= 73)	Eylea 2 mg (N = 114)	Control[E)] (N =73)	Eylea[F)] 2 mg (N= 114)	Control[E,F)] (N=73)	Eylea 2 mg Q4 (N = 103)	Control (N = 68)	Eylea 2 mg (N = 103)	Control (N = 68)	Eylea[G)] 2 mg (N = 103)	Control[G)] (N = 68)

Proportion of patients who gained at least 15 letters in BCVA[C)] from baseline	56%	12%	55%	30%	49.1%	23.3%	60%	22%	60%	32%	57.3%	29.4 %
Weighted difference[A, B,E)] (95% CI)	44.8% (33.0, 56.6)		25.9% (11.8, 40.1)		26.7% (13.1, 40.3)		38.3% (24.4, 52.1)		27.9% (13.0, 42.7)		28.0% (13.3, 42.6)	
p-value	p < 0.0001		p = 0.0006		p=0.0003		p < 0.0001		p = 0.0004		p=0.0004	
Mean change in BCVA as measured by ETDRS[C)] letter score from baseline (SD)	17.3 (12.8)	-4.0 (18.0)	16.2 (17.4)	3.8 (17.1)	13.0 (17.7)	1.5 (17.7)	18.0 (12.2)	3.3 (14.1)	16.9 (14.8)	3.8 (18.1)	13.7 (17.8)	6.2 (17.7)
Difference in LS mean[A,C,D,E)] (95% CI)	21.7 (17.4, 26.0)		12.7 (7.7, 17.7)		11.8 (6.7, 17.0)		14.7 (10.8, 18.7)		13.2 (8.2, 18.2)		7.6 (2.1, 13.1)	
p-value	p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001		p=0.0070	

[A)] Difference is Eylea 2 mg Q4 weeks minus control
[B)] Difference and confidence interval (CI) are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)
[C)] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
SD: Standard deviation
LS: Least square means derived from ANCOVA
[D)] LS mean difference and confidence interval based on an ANCOVA model with factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)
[E)] In COPERNICUS study, control group patients could receive Eylea on an as-needed basis as frequently as every 4 weeks during week 24 to week 52; patients had visits every 4 weeks.
[F)] In COPERNICUS study, both control group and Eylea 2mg patients received Eylea 2 mg on an as-needed basis as frequently as every 4 weeks starting from Week 52 to Week 96; patients had mandatory quarterly visits but may have been seen as frequently as every 4 weeks if necessary.
[G)] In GALILEO study, both control group and Eylea 2mg patients received Eylea 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68; patients had mandatory visits every 8 weeks.

Figure 2: Mean change from baseline to week 76/100 in visual acuity by treatment group for the COPERNICUS and GALILEO studies (Full Analysis Set)



The proportion of perfused patients in the Eylea group was high in the GALILEO study at baseline 86.4%; (n = 89). Perfusion at week 24 primary endpoint was 91.8% (n = 89). The patients were largely able to maintain their perfusion status until week 76 84.3%; (n = 75). The number of perfused patients that started on sham was

79.4% (n = 54) at baseline. Perfusion at week 24 primary endpoint was 85.5% (n = 47). Patients in the sham group were switched to Eylea according to pre-specified criteria at week 52, 83.7% (n = 41) were perfused at this time. The patients were able to maintain their perfusion status until week 76, 84.0% (n = 42).

The proportion of perfused patients in the Eylea group in the COPERNICUS study at baseline was 67.5% (n = 77). Perfusion at week 24 primary endpoint was 87.4%; (n = 90). After week 24, patients in the Eylea group were treated according to pre-specified criteria. At week 100 76.8 % (n = 76) of patients were perfused. The percentage of perfused patients that started on sham was 68.5% (n = 50) at baseline. Perfusion at week 24 primary endpoint was 58.6% (n = 34). Patients in the sham arm were eligible to receive Eylea from week 24. The proportion of perfused patients increased to 83.9% (n = 47) at week 52 and was largely maintained until week 100 78%; (n = 39). The beneficial effect of Eylea treatment on visual function was similar in the baseline subgroups of perfused and non-perfused patients.

In combined data analysis of the GALILEO and COPERNICUS studies, Eylea demonstrated clinically meaningful changes from baseline in pre-specified secondary efficacy endpoint National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in Best Corrected Visual Acuity (BCVA).

Treatment effects in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, retinal perfusion status, CRVO duration) in each study were in general consistent with the results in the overall populations.

Elderly population

In the CRVO studies, approximately 52% (112/217) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 18% (38/217) were 75 years of age or older.

Macular Oedema secondary to BRVO

The safety and efficacy of Eylea were assessed in a randomised, multi-centre, double-masked, active-controlled study in patients with macular oedema secondary to BRVO which included Hemi-Retinal Vein Occlusion. A total of 181 patients were treated and evaluable for efficacy (91 with Eylea) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg Eylea administered every 8 weeks following 6 initial monthly injections or laser photocoagulation administered at baseline (laser control group). Patients in the laser control group could receive additional laser photocoagulation (called 'rescue laser treatment') beginning at week 12, if needed. The minimum interval between laser photocoagulation treatments was 12 weeks. Beginning at week 24, patients in the laser treatment group could receive rescue treatment with Eylea 2mg, if needed, administered every 4 weeks for 3 months followed by intravitreal injections every 8 weeks, based on pre-specified criteria.

Patient ages ranged from 42 to 94 years with a mean of 65 years.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. At week 24, the Eylea group was superior to laser control for the primary endpoint.

Change in visual acuity at week 24 compared to baseline was a secondary efficacy variable in the VIBRANT study. The difference between treatment groups was statistically significant in favour of Eylea. The course of visual improvement was rapid and maximal improvement was achieved at month 3 with subsequent stabilisation of the effect on visual acuity and central retinal thickness until month 6 and subsequent maintenance of the effect until month 12.

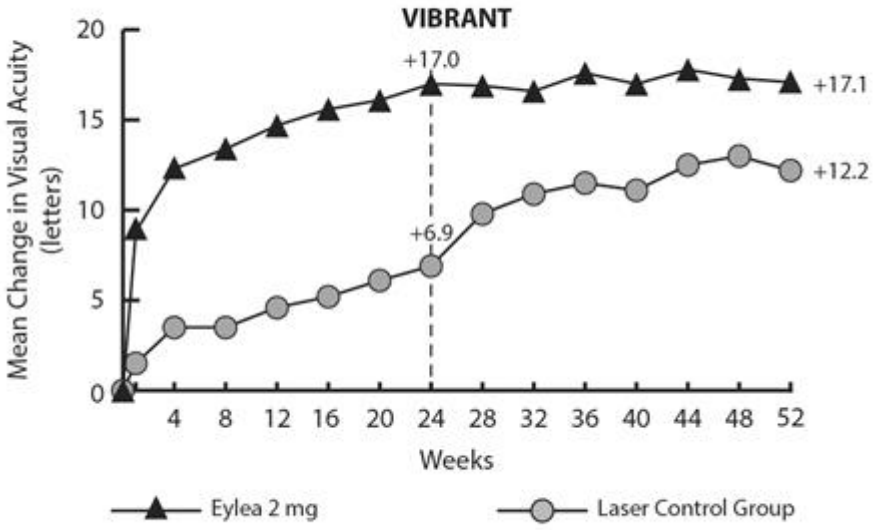
In the laser group 67 patients received rescue treatment with Eylea beginning at week 24 (Active Control/ Eylea 2mg group). In this treatment group visual acuity improved by about 5 letters from week 24 to 52.
Detailed results from the analysis of the VIBRANT study are shown in the Table 4 and Figure 3 below.

Table 4: Efficacy outcomes at week 24 and week 52 (Full Analysis Set with LOCF) in VIBRANT study (Bayer plc., 2015)

Efficacy Outcomes	**VIBRANT**			
	24 weeks		**52 weeks**	
	Eylea 2mg Q4 (N = 91)	**Active Control (laser) (N = 90)**	**Eylea 2mg Q8 (N = 91)[D)]**	**Active Control (laser)/Eylea 2mg[E)] (N = 90)**
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	52.7%	26.7%	57.1%	41.1%
Weighted Difference [A,B] (%) (95% CI) p-value	26.6% (13.0, 40.1) p=0.0003		16.2% (2.0, 30.5) p=0.0296	
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	17.0 (11.9)	6.9 (12.9)	17.1 (13.1)	12.2 (11.9)
Difference in LS mean [A,C] (95% CI) p-value	10.5 (7.1, 14.0) p<0.0001		5.2 (1.7, 8.7) p=0.0035[F)]	

[A)] Difference is Eylea 2 mg Q4 weeks minus Laser Control
[B)] Difference and 95% CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)
[C)] LS mean difference and 95% CI based on an ANCOVA model with treatment group, baseline BCVA category (> 20/200 and ≤ 20/200) and region (North America vs. Japan) as fixed effects, and baseline BCVA as covariate
[D)] From Week 24 on the treatment interval in the Eylea treatment group was extended for all subjects from 4 weeks to 8 weeks through week 48.
[E)] Beginning at Week 24 subjects in the Laser Group could receive rescue treatment with Eylea, if they met at least one pre-specified eligibility criterion. At total of 67 subjects in this group received Eylea rescue treatment. The fixed regimen for Eylea rescue was three times Eylea 2mg every 4 weeks followed by injections every 8 weeks.
[F)] Nominal p-value

Figure 3: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 52 in VIBRANT Study



At baseline, the proportion of perfused patients in the Eylea and laser groups was 60% and 68%, respectively. At week 24 these proportions were 80% and 67%, respectively. In the Eylea group the proportion of perfused patients was maintained through week 52. In the laser group, where patients were eligible for rescue treatment with Eylea from week 24, the proportion of perfused patients increased to 78% by week 52.

Elderly population

In the BRVO study, approximately 58% (53/91) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 23% (21/91) were 75 years of age or older.

Diabetic Macular Oedema

The safety and efficacy of Eylea were assessed in two randomised, multi-center, double-masked, active-controlled studies in patients with DME. A total of 862 randomised and treated patients were evaluable for efficacy. Of those, 576 were

randomised to the Eylea groups in two studies (VIVID[DME] and VISTA[DME]). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens:

1) Eylea administered 2 mg every 8 weeks following 5 initial monthly injections (Eylea 2Q8);
2) Eylea administered 2 mg every 4 weeks (Eylea 2Q4); and
3) macular laser photocoagulation (active control).

Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the Eylea groups could receive laser and patients in the laser group could receive Eylea. Patient ages ranged from 23 to 87 years with a mean of 63 years. The majority of patients in both studies had Type II diabetes.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52 as measured by ETDRS letter score. Both Eylea 2Q8 and Eylea 2Q4 groups were shown to have efficacy that was statistically significantly superior to the laser control group. Detailed results from the analysis of the VIVID[DME] and VISTA[DME] studies are shown in Table 5 and Figure 4 below.

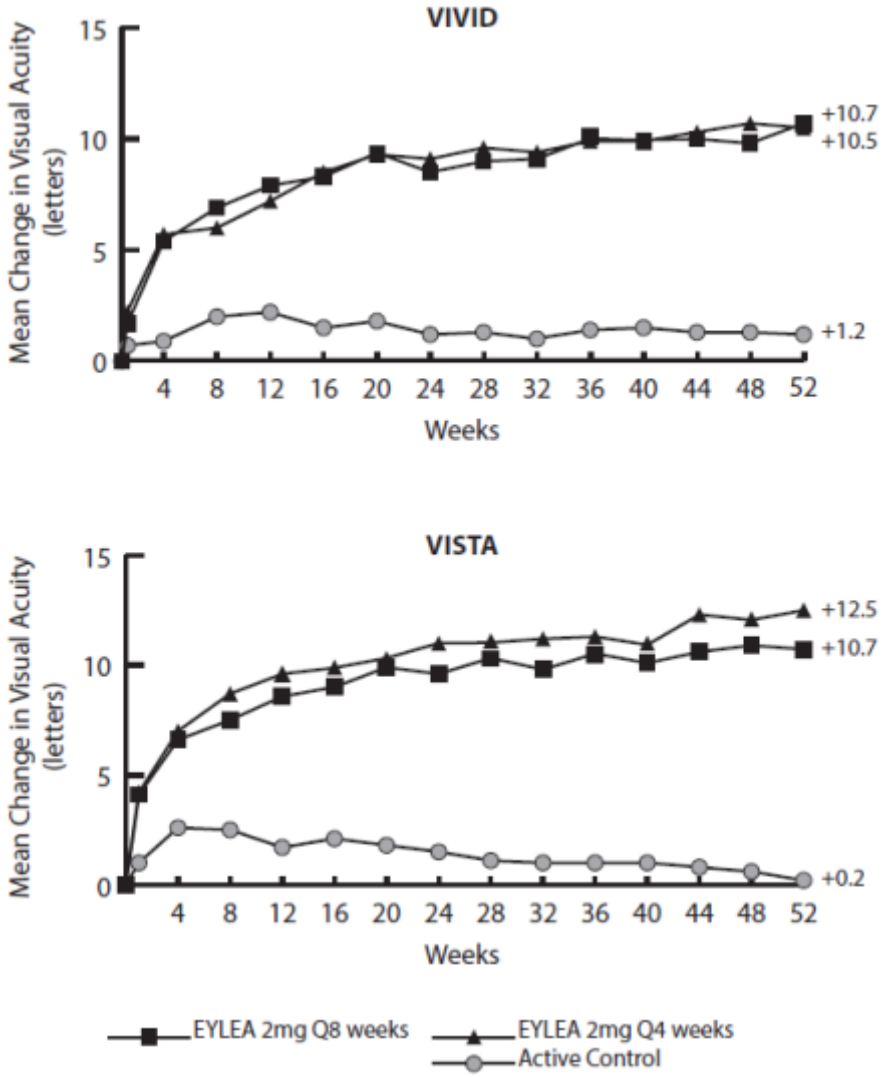
Table 5: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIVID[DME] and VISTA[DME] Studies (Bayer plc., 2015)

Efficacy Outcomes	**VIVID[DME]**			**VISTA[DME]**		
	52 Weeks			**52 Weeks**		
	Eylea 2 mg Q8 [A] (N = 135)	**Eylea 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**	**Eylea 2 mg Q8 [A] (N = 151)**	**Eylea 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**
Mean change in BCVA as measured by ETDRS [E] letter score from Baseline	10.7	10.5	1.2	10.7	12.5	0.2
Difference in LS mean [B,C,E] (97.5% CI)	9.1 (6.3, 11.8)	9.3 (6.5, 12.0)		10.45 (7.7, 13.2)	12.19 (9.4, 15.0)	
Proportion of patients who gained at least	33%	32%	9%	31%	42%	8%

15 letters in BCVA [E] from Baseline						
Adjusted Difference [D,C,E] (97.5% CI)	24% (13.5, 34.9)	23% (12.6, 33.9)		23% (13.5, 33.1)	34% (24.1, 44.4)	

[A] After treatment initiation with 5 monthly injections
[B] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as factor for VIVID^{DME}, and history of MI and/or CVA as a factor for VISTA^{DME}).
[C] Difference is Eylea group minus active control (laser) group
[D] Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by region (Europe/Australia vs. Japan) for VIVID^{DME} and medical history of MI or CVA for VISTA^{DME}
[E] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
LS: Least square means derived from ANCOVA
CI: Confidence interval

Figure 3: Mean change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 52 in VIVID^{DME} and VISTA^{DME} Studies (Bayer plc., 2015)



The VISTA^{DME} second year outcomes are in line with the results from the primary and secondary endpoints obtained at week 52.
Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study and in the combined analysis were generally consistent with the results in the overall populations.

In the VIVID^{DME} and VISTA^{DME} studies, 36 (9%) and 197 (43%) patients received prior anti-VEGF therapy, respectively, with a 3-month or longer washout period. Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Patients with bilateral disease were eligible to receive anti-VEGF treatment in their fellow eye if determined to be necessary by the physician. In the VISTA^{DME} study, 198 (65%) of Eylea patients received bilateral Eylea injections; in the VIVID^{DME} study, 70 (26%) of Eylea patients received a different anti-VEGF treatment in their fellow eye.

Elderly population

In the DME phase III studies, approximately 47% (268/576) of the patients randomised to treatment with Eylea were 65 years of age or older, and approximately 9% (52/576) were 75 years of age or older. Efficacy and safety outcomes were consistent with the outcomes of the overall population.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Eylea in all subsets of the paediatric population in wet AMD, CRVO, BRVO and DME (see section 4.2 for information on paediatric use).

3.5 Assessment and management of risk

Risk management:

Risk*	How the risk will be minimised
Sub-conjunctival haemorrhage	Avoid injecting around vascular area
Endophthalmitis	Perform intravitreal injection (IVT) under aseptic conditions. Provide patients with post-IVT anti-biotic drops
Intraocular inflammation	Exclude patients with active severe intraocular inflammation
Rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract	Perform IVT at 3.5mm from the limbus in pseudo-phakic patients and 4.0mm from the limbus in phakic patients
Non-ocular haemorrhages and arterial thromboembolic events	Exclude patients who have suffered a thromboembolic event (MI/CVA/Unstable Angina) within 3 months
Raised intra-ocular pressure	Exclude patients with uncontrolled IOP >24mmHg for

	ocular hypertension (on topical IOP lowering medications) or those with advanced glaucoma (in the opinion of a glaucoma specialist). IOP check to be performed before the patient goes home on the day of IVT.

*Risks as per current use in wet AMD and macular oedema secondary to CRVO, BRVO and DMO.

Logistics

All patients will receive 3 loading injections of Eylea at monthly intervals followed by a treat and extend protocol up to 12 months.

Extension from monthly to 6, 8 and 12 week follow-up will occur when there is evidence of OCT stability in the view of the investigator i.e. there is no further reduction in macular fluid compared to the previous visit.

Injections will be administered by Dr. Stacey Strong (Clinical Research Fellow) who is experienced in the administration of intravitreal injections. If, for any reason, Dr. Strong is absent on a day that a patient has a scheduled visit, another clinical trial fellow who is also GCP trained and experienced in the administration of intravitreal injections will be appointed to perform the procedure. Decisions regarding extension from monthly to 6, 8 and 12 weeks will be taken in consultation with Professor Michel Michaelides. All injections will be carried out at the Clinical Research Facility, Moorfields Eye Hospital.

This trial is categorised as:

• Type B = Somewhat higher than the risk of standard medical care

(being an invasive procedure rather than the current treatment of oral/topical medications)

4 Objectives

To assess the efficacy and safety of Eylea in patients with Retinitis Pigmentosa associated with cystoid macular oedema.

Primary Objective: To report mean Central Macular Thickness (CMT) at 12 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

Secondary Objectives:

To report mean Central Macular Thickness (CMT) at 6 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

To report mean change in Central Macular Thickness (CMT) as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months.

To report the mean BCVA ETDRS letter score at 6 and 12 months in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

To report the mean change in BCVA ETDRS letter score in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and 6 months, and baseline and twelve months.

To report mean macular volume at 6 and 12 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

To report mean change in macular volume as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months.

To report all AEs and SAEs at any time point during the 12 month study of using intravitreal Eylea in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema.

To report the mean retinal sensitivity at 6 and 12 months using Microperimetry in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

To report the mean change in retinal sensitivity using Microperimetry in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and 6 months, and baseline and twelve months

To report the mean number of intravitreal injections administered in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

5 Trial design

5.1 Overall design

- Purpose of research:

To assess the safety and efficacy of Eylea in patients with Retinitis Pigmentosa associated with cystoid macular oedema.

- Trial design
  - Open label, prospective, non-randomised
  - 30 patients with RP associated CMO
  - 16 years of age
  - Molecularly confirmed patients prioritised (to be able to potentially explore any pharmacogenetic aspects)
  - Recruited over a 9 month period, with each patient having 12 month follow-up
  - All patients receive 3 loading injections of Eylea at monthly intervals followed by a treat and extend protocol up to 12 months
  - Extension from monthly to 6, 8 and 12 week follow-up will occur when there is evidence of OCT stability in the view of the investigator i.e. there is no further reduction in macular fluid compared to the previous visit
  - All patients will receive 5 injections before considering them non-responders
  - BCVA and SDOCT undertaken at every visit
  - Microperimetry undertaken at Baseline, 6 months and 12 months
  - Fundus Autofluorescence (FAF) Imaging Baseline, 6 and 12 months
  - Refracted BCVA at baseline, 6 months and 12 months
  - SDOCTs will be graded by Moorfields Eye Hospital Reading Centre

6 Selection of Subjects

6.1 Inclusion criteria

- CMO in association with RP
- ≥ 16 years of age
- Unilateral or Bilateral CMO (the worse eye only will be treated – defined as the eye with a greater central macular thickness (CMT) on OCT)
- No previous oral treatment for CMO for last 3 months
- No previous peribulbar or intravitreal treatment for CMO in the study eye for last 3 months
- No previous topical treatment for CMO in the study eye for last 1 month
- Central visual impairment that in the view of the Principal Investigator is due to CMO
- BCVA better than 3/60

6.2 Exclusion criteria

- Insufficient patient cooperation or media clarity to allow adequate fundus imaging.
- Evidence of visually significant vitreo-retinal traction or epiretinal membrane on OCT that in the Principal Investigator's opinion is highly likely to significantly limit the efficacy of intravitreal therapy.
- History of cataract surgery within prior 3 months or cataract surgery anticipated within 6 months of starting the study.
- Any anti-VEGF treatment to study eye within 3 months.
- History of YAG capsulotomy performed within 3 months.
- Uncontrolled IOP > = 24 mmHg for ocular hypertension (on topical IOP lowering medications)
- Advanced glaucoma (in the opinion of a glaucoma specialist).

- Patients with active or suspected ocular or periocular infections
- Patients with active severe intraocular inflammation.
- Patients with a new, untreated retinal tear or detachment
- Patients with a stage 3 or 4 macular hole
- Thromboembolic event (MI/CVA/Unstable Angina) within 6 months.
- Pregnancy or family planned within 15 months
- Females who are breast feeding
- Known allergy or hypersensitivity to anti-VEGF products

Females of childbearing potential and males must be willing to use an effective method of contraception (hormonal or barrier method of birth control; abstinence) from the time consent is signed until 12 weeks after treatment discontinuation. The MHRA advise double contraception.

Females of childbearing potential must have a negative pregnancy test within 7 days prior to being registered for trial treatment. NOTE: Subjects are considered not of child bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal.

7 Recruitment

Patients will be approached at medical retina clinics at Moorfields Eye Hospital, or contacted by phone, email or post.

8 Study procedures and schedule of assessments

8.1 Informed consent procedure

Dr. Stacey Strong is GCP trained, suitably qualified and experienced to deliver intravitreal injections and be delegated the duty of taking informed consent by the CI/PI (Professor Michel Michaelides). Written informed consent will be obtained from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

"Adequate time" must be given for consideration by the patient before taking part. The PI must record when the patient information sheet (PIS) has been given to the patient. The Investigator or designee will explain the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into trial.

A copy of the signed Informed Consent form will be given to the participant. **The original** signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate

8.2 Randomisation procedures

Non-applicable as this is a non-randomised trial

8.3 Unmasking

Non-applicable as this is an open label trial

8.4 Screening Period

Patients will be recruited over a 6 to 12 month period. Within a week of being approached in the medical retina clinics or by telephone and having been provided with information about the trial, our research manager will contact the patient and invite them to attend a screening appointment. This screening appointment ('Screening') should occur within 28 days of being contacted. At the screening appointment the patient will have the opportunity to ask any further questions before informed consent is taken, their medical/drug history reviewed, a general physical examination performed together with vital signs including blood pressure and temperature measurements. If they are deemed fit to enter the trial, their 1st Eylea intravitreal injection will be given on the same day ('Visit 1').

a. Screening visit to take place within 28 days of being contacted by research manager

b. If for any reason the patient cannot attend their scheduled visit, an alternative appointment will be arranged. This must occur within 14 days of the original scheduled date.

c. The follow up period should be 28 days after Visits 1 and 2. The follow up period after visit 3 will depend on whether there is evidence of OCT stability in the view of the investigator (i.e. there is no further reduction in macular fluid compared to the previous visit) in which case extension from 4 to 6, 8 and 12 week follow up will occur.

d. Follow up will occur up until 12 months after the first treatment was initiated.

Screen failures i.e. patients who do not meet eligibility criteria at time of screening may be eligible for rescreening subject to acceptable parameters. For example, if a

patient was breast-feeding at the initial screening and decided to stop a few months later, she could be invited for a second screening appointment.

8.5 Baseline and subsequent assessments

	Screening and Baseline	Treatment phase and follow-up*											
Weeks	Baseline	4 wks post baseline	8 wks post baseline	12 wks post baseline	4 - 12 wks post visit 4	4 - 12 wks post visit 5	4 - 12 wks post visit 6	4 - 12 wks post visit 7	4 - 12 wks post visit 8	4 - 12 wks post visit 9	4 - 12 wks post visit 10	4 - 12 wks post visit 11	4 - 12 wks post visit 12
Patient demographics confirmed	X	X	x	X	x	x	x	x	x	x	x	x	X
General medical and ocular history	X												
Medication review	X	x	x	x	x	x	x	x	x	x	x	x	X
Pregnancy status confirmed	X												
Eligibility check	X												
Informed Consent	X												
Vital signs: Blood pressure, heart rate and temperature	X	X	x	X	x	x	x	x	x	x	x	x	X
Best corrected ETDRS visual acuity	X	X	X	X	x	x	x	x	x	x	x	x	x
Refracted best corrected ETDRS visual acuity	X					X (at 6 months)							X (at 12 months)
Colour vision	X	X	X	X	x	x	x	x	x	x	x	x	x
Contrast sensitivity	X	X	X	X	x	x	x	x	x	x	x	x	x
Microperimetry	X					X (at 6 months)							X (at 12 months)
Dilation of the patient	X	X	X	X	x	x	x	x	x	x	x	x	x
Slit lamp examination	X	X	X	X	x	x	x	x	x	x	x	x	x
IOP check (pre-injection)	X	X	X	X	x	x	x	x	x	x	x	x	x
SDOCT in both eyes	X	X	X	X	x	x	x	x	x	x	x	x	x
Fundus Autofluorescence	X					X(at 6 months)							x
Administration of Eylea	Possibly	X	X	X	x	x	x	x	x	x	x	x	x
IOP check (post-injection)	X	X	X	X	x	x	x	x	x	x	x	x	x

***Number of total visits will vary between patients as follow-up appointments will be any time between 4 – 12 weeks.**

8.6 Treatment procedures

Eylea 2 mg (0.05mL) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 4-12 weeks depending on whether there is evidence of OCT stability in the view of the investigator (i.e. there is no further reduction in macular fluid compared to the previous visit)

8.7 Flowchart of study assessments

Patient demographics confirmed (at all scheduled visits)
General medical and ocular history (taken at baseline only)
Medication review (at all scheduled visits)
Pregnancy status confirmed (taken at baseline only)
Eligibility check (taken at baseline only)
Informed consent (taken at baseline only)
Vital signs inc: blood pressure, heart rate and temperature (at all scheduled visits)
BCVA (at all scheduled visits)
Refracted BCVA (Baseline, 6 and 12 months)
Colour vision (at all scheduled visits)
Contrast Sensitivity (at all scheduled visits)
Microperimetry (Baseline, 6 and 12 months)
Dilation of the patient (at all scheduled visits)
Slit lamp examination to check for cataract (at all scheduled visits)
Pre-injection IOP check (at all scheduled visits)
SDOCT (at all scheduled visits)
Fundus Autofluorescence Imaging (Baseline, 6 and 12 months)
Administration of Eylea (at all scheduled visits)
Post-injection IOP check (at all scheduled visits)

8.8.1 Laboratory procedures

No samples are to be processed for this trial

8.9 Definition of end of trial

28 days following the last visit by the last participant.

8.10 Discontinuation/withdrawal of participants and 'stopping rules'

Circumstances in which subjects will be withdrawn from the trial, include: Mortality, CVA/TIA/MI/Unstable angina, Hypersensitivity/Allergy to anti-VEGF and if for any reason the patient no longer wishes to be involved with the trial. This will be confirmed in writing and documentation sent to both patient and GP informing them why they have been withdrawn from the trial and thanking them for their participation up to that point. Withdrawn subjects will only be replaced if their withdrawal is deemed unrelated to the trial, for example, if a patient needs to relocate for work purposes/sick family member and can no longer physically attend their appointments. Replacement patients will be recruited in an identical fashion to those who originally enrolled in the study. Recruitment of these patients must occur within the designated 8 month recruitment period. Patients who withdraw for reasons deemed related to the trial e.g. intolerable side effects, will not be replaced. Patients who withdraw from the study will be asked to attend an exit follow-up review at 12 months, which will involve the same tests to be undertaken as those still remaining in the study.

In the event of a retinal break the dose should be withheld and treatment should not be resumed until the break is adequately repaired

The trial will be stopped prematurely:

1) if serious adverse effects are shown to be caused by Eylea and the trial safety is deemed to have unacceptable

9 Name and description of all drugs used in the trial

Eylea:

Eylea is currently licenced for use in wet AMD and Macular Oedema secondary to CRVO, BRVO and DMO. Please see below for information regarding safety and efficacy of Eylea. There is some evidence in the literature that anti-VEGF therapy may be effective in patients with Reitnitis Pigmentosa associated with cystoid macular oedema – Artunay et al (Journal of Ocular Pharmacology and Therapeutics 2009,25(6)545-550) observed significant response to a single injection of Lucentis in 15 eyes of 15 patients with RP and CMO over a 6 month follow-up period. By undertaking the proposed protocol-driven prospective study we will obtain reliable data to potentially plan a randomised controlled trial – potentially multi-centre.

Mechanism of action - 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. 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.

Tropicamide 1% eye drops:

Tropicamide is an eye drop used to dilate (enlarge) the pupil of the eye. This allows for easier examination of the back of a patients eye by an eye doctor. Tropicamide

also effects the muscle that controls the lens of the eye, which results in reduced accommodation (being able to focus on close objects). Due to the effects of tropicamide, some people may find bright light uncomfortable and have blurred vision, which may affect the ability to drive. The effects of tropicamide are only temporary lasting between 4-6 hours, however, it is possible for the effects to last longer.

Each carton of tropicamide contains 20 minim units, measuring approximately 0.5ml of the active ingredient tropicamide 1% w/v (5mg). Other ingredients are sodium hydroxide, hydrochloric acid (for pH adjustment) and purified water. There is no preservative.

Tropicamide should not be used in patients with known allergy to tropicamide or any of its ingredients. It should also not be used in patients with a history of closed angle glaucoma (a particular type of glaucoma) or patients with a narrow chamber at the front of the eye. This can be confirmed on examinaton by the doctor prior to its usage. Tropicamide can cause temporary stinging upon its administration into the eye. It is also possible for this medication to cause a patient to have a dry mouth.

Phenylepherine 2.5% eye drops:

Phenylepherine 2.5% is an eye drop used to dilate (enlarge) the pupil of the eye. This allows for easier examination of the back of a patients eye by an eye doctor. Due to the effects of phenylephrine, some people may find bright light uncomfortable and have blurred vision, which may affect the ability to drive. The effects of phenylepherine are only temporary lasting between 4-6 hours, however, it is possible for the effects to last longer.

Each carton of phenylephrine 2.5% contains 20 minim units, measuring approximately 0.5ml solution of phenylephrine hydrochloride 2.5% w/v (12.5mg).

Other ingredients are sodium metabisulphite (E223), disodium edetate and purified water. There is no preservative.

Phenylepherine should not be used in patients with known allergy to phenylepherine or any of its ingredients. It should also not be used in patients with a history of heart disease, fast heartbeats (tachycardia), high blood pressure, bulges in major blood vessels (aneurysms), overactive thyroid gland (hyperthyroidism) or high sugar level (diabetes mellitus). It should also not be used in patients with a history of closed angle glaucoma (a particular type of glaucoma) or patients with a narrow chamber at the front of the eye. This can be confirmed on examination by the doctor prior to its usage.

Proxymetacaine eye drops:

Proxymetacaine is an eye drop used before the giving of an intravitreal injection, in order to produce an anaesthetic effect on the eye. Each pack contains 20 units (minims) containing the active ingredient Proxymetacaine Hydrochloride. Each unit contains approximately 0.5 ml eye drops solution of proxymetacaine hydrochloride 0.5% (2.5 mg). The other ingredients are hydrochloric acid, sodium hydroxide and purified water. This medicine does not contain a preservative as it is a sterile single use unit.

Allergic reactions can occasionally occur that affect the cornea (a transparent membrane covering the iris and pupil of the eye) and the iris. The following reactions have been reported very rarely and usually wear off quickly:

- widening of the pupil (center of the iris)
- transient loss of lens movement (inability to read)
- irritation of the conjunctiva (a membrane which lines the inside of the eyelid)

In rare circumstances, a defect or inflammation of the cornea (whitening of the deep cornea, immunology-mediated disorder) and/or inflammation of the iris may occur.

Iodine eye drops and skin preparation

Iodine has a powerful bactericidal action and is used for disinfecting unbroken skin before operations. Iodine is active against fungi, viruses, protozoa, cysts and spores. The product is suitable for use by adults, children and the elderly. Excipients include: purified water and ethanol (96%). Its use is contraindicated in patients with hypersensitivity to iodine or iodides, newborn infants and in patients with thyroid disorders or those receiving lithium therapy.

Allergic reactions that can occur, include: urticaria, angioedema, cutaneous haemorrhage or purpuras, fever, arthralgia, lymphadenopathy and eosinophilia.

Chloramphenicol eye drops

Chloramphenicol eye drops will be prescribed to each patient in order to prevent an infection occurring following intravitreal injection. It will be prescribed for use four times a day to the treated eye, for a total of 5 days. It is contra-indicated for use in patients with a known hypersensitivity to chloramphenicol or to any other component of the preparation and if there is a family or personal history of blood dyscrasias including aplastic anaemia.

Adverse local effects: Sensitivity reactions such as transient irritation, burning, stinging, itching and dermatitis have been reported. Sometimes the eye drops can be tasted or affect taste as they drain from the eye into the back of the mouth. The prolonged use of eye drops containing a phenylmercuric preservative has been associated with skin irritation, primary atypical band keratopathy (changes to the cornea) and mercurialentis (pigmentation of the anterior capsule of the lens).

Adverse systemic effects: Rarely cases of adverse haematological events (bone marrow depression, aplastic anaemia and death) have been reported following ocular use of chloramphenicol.

9.1 Concomitant medication

No interaction studies have been performed, however, medication(s)/treatment(s) not permitted before and/or during the trial (specify time restrictions) include:

- Any intravitreal (anti-VEGF) treatment to the study eye within 3 months of starting the trial or during the trial itself
- Any oral carbonic anhydrase inhibitors within 3 months of starting the trial or during the trial itself
- Any topical carbonic anhydrase inhibitors to the study eye within 1 month of starting the trial or during the trial itself
- Any peri-bulbar treatment to the study eye within 3 months of starting the trial or during the trial itself

Medication(s)/treatment(s) permitted before and/or during the trial (specify time restrictions) include:

- Any intravitreal (anti-VEGF) treatment to the study eye given more than 3 months before the 1st injection of Eylea is due to take place
- Any oral carbonic anhydrase inhibitors taken more than 3 months before the 1st injection of Eylea is due to take place
- Any topical carbonic anhydrase inhibitors taken more than 1 month before the 1st injection of Eylea is due to take place. It may be used throughout the trial in the non-study eye.
- Any peri-bulbar treatment to the study eye given more than 3 months before the 1st injection of Eylea is due to take place
- Any medication that the patient was on before the trial started, or is required to take during the trial period, as long as it is not in the list mentioned above

10 Investigational Medicinal Product

10.1 Name and description of Investigational Medicinal Product(s)

Eylea solution is supplied in a vial (40mg/ml). Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept. The dose used in this trial will be 0.05ml (2mg) per intravitreal injection and will be supplied free of charge by the manufacturer Bayer plc. Eylea is already licenced for use in these quantities for wet AMD and oedema secondary to CRVO, BRVO and DMO. Please see section 3.4.

10.2 Name and description of each Non-IMP (NIMP)

N/A

10.3 Summary of findings from non-clinical studies

Please refer to:
https://www.medicines.org.uk/emc/medicine/27224/SPC/Eylea+40mg+ml+solution+for+injection+in+a+vial/

10.4 Summary of findings from clinical studies

Please refer to:
https://www.medicines.org.uk/emc/medicine/27224/SPC/Eylea+40mg+ml+solution+for+injection+in+a+vial/

10.5 Summary of known and potential risks and benefits

Please refer to:
https://www.medicines.org.uk/emc/medicine/27224/SPC/Eylea+40mg+ml+solution+for+injection+in+a+vial/

10.6 Description and justification of route of administration and dosage

Eylea is a solution that needs to be placed in the vitreous cavity of the eye in order for it to have localised effects with minimal systemic absorption. This is achieved in the form of an intravitreal injection. No other form of drug delivery is deemed acceptable in this trial.

10.7 Dosages, dosage modifications and method of administration

Please see the following link for The Royal College of Ophthalmologist Guidelines for Intravitreal Injections Procedure (2009): https://www.rcophth.ac.uk/wp-content/uploads/2015/01/2009-SCI-012_Guidelines_for_Intravitreal_Injections_Procedure_1.pdf

Eylea solution is supplied in a vial (40mg/ml). Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. A 23G blue needle is fitted onto a 1ml insulin syringe and the entire contents of the vial withdrawn. Care is taken to expel any air bubbles from the syringe. The 23G blue needle is then replaced with a 30G needle and any excess drug expelled until exactly 0.05ml is contained within the syringe. The contents are injected into the vitreous cavity of the eye using an infero-temporal approach as a first preference. This will be 3.5mm away from the limbus in pseudo-phakic patients, and 4mm away from the limbus in phakic patients. No reconstitution is required. This dose remains identical for any injection of Eylea that is given. All patients will receive 3 loading injections of Eylea at monthly intervals followed by a treat and extend protocol up to 12 months.

Extension from monthly to 6, 8 and 12 week follow-up will occur when there is evidence of OCT stability in the view of the investigator i.e. there is no further reduction in macular fluid compared to the previous visit.

10.8 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of the investigational medicinal products will be completed in accordance with the relevant GMP guidelines. Text for labels used for the Investigational Medicinal Product may be obtained by the Pharmacist.

Due to the primary packaging containing a small vial of medication on which particulars cannot be displayed, a second sheet will bear a label containing the following information:

(a) name of sponsor, or investigator
(b) route of administration, the name/identifier and strength/potency
(c) batch and/or code number to identify the contents and packaging operation;
(d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere
(e) the trial subject identification number/treatment number and where relevant, the visit number

10.9 Drug accountability

The drug, Eylea, will be provided by the manufacturer Bayer who will be responsible for the shipment and receipt of the product. All units will be held at the pharmacy within Moorfields Eye Hospital. The contact person is Racheal Yoon (racheal.yoon@moorfields.nhs.uk). Once the product has been used, the glass vial and any sharps will be disposed of into a designated yellow sharps bin located within the treatment room of the clinical research facility. Any unused vials will be returned to the manufacturer or destroyed.

10.10 Source of IMPs including placebo

The drug Eylea will be provided for use in this trial at no cost to the hospital.

10.11 Dose modifications

All patients will receive 3 loading injections of Eylea at monthly intervals followed by a treat and extend protocol up to 12 months. Each injection will contain 2mg of the active ingredient. Extension from monthly to 6, 8 and 12 week follow-up will occur when there is evidence of OCT stability in the view of the investigator i.e. there is no further reduction in macular fluid compared to the previous visit.

In the case of a serious adverse event, no further injections of Eylea will be given.

10.12 Assessment of compliance

Compliance includes both adherences to IMP and Protocol study procedures.

Noncompliance to the Protocol study procedures will be documented by the investigator and reported to the Sponsor as agreed. Persistent noncompliance may lead the patient to be withdrawn from the study.

Procedures defined for:

- Monitoring: Patient will be observed having intravitreal injection
- Recording of subject compliance: date of attendance will be recorded
- Details of follow-up of non-compliant subjects: A list of patients that have been deemed to be non-compliant will be kept. Non-compliant patients will be invited to attend an Exit Visit at 12 months post initial intravitreal injection.

10.13 Post-trial IMP arrangements

Even if the results of this trial were favourable, the drug would still likely need to undergo further testing using a multi-centre placebo-controlled approach in order to consider licencing of the product for use in RP associated CMO. Patients involved in the trial will therefore be unable to continue receiving Eylea at the end of the trial. Patients will continue to be seen in their regular clinics, where a decision will be taken by the team, whether previous treatment should be re-started or not.

11 Recording and reporting of adverse events and reactions

11.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which **is related** to any dose administered to that subject. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*

Term	Definition
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
SUSAR	Suspected Unexpected Serious Adverse Reaction

11.2 Recording adverse events

All adverse events will be recorded in the medical records, Case Report Form (CRF) and Adverse Event form following consent.

If the investigator suspects that the subjects' disease has progressed faster due to the administration of Eylea, it will be recorded and reported as an unexpected adverse event.

Clinically significant abnormalities in the results of objective tests (e.g. visual acuity, temperature, blood-pressure) will also be recorded as adverse events. If the results are not expected as part of disease or from the injection of Eylea in accordance with the SPC, these will also be recorded as unexpected.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All adverse events will be recorded until 12 months post 1st IVT.

Each adverse event will be assessed for the following criteria:

11.2.1 Severity

Category	Definition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

11.2.2 Causality

The assessment of relationship of adverse events to the administration of Eylea is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).

Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

11.2.3 Expectedness

Category	Definition
Expected	An adverse event the nature or severity of which is consistent with the information about Eylea listed in the Investigator Brochure (or SmPC if Licensed IMP) **or clearly defined in this protocol.**
Unexpected	An adverse event, the nature or severity of which is not consistent with the information about Eylea listed in the Investigator Brochure (or SmPC if Licensed IMP)

11.2.4 Seriousness

All AEs/ARs will be assessed to see is they meet the definition of serious as per section 11.1

11.3 Procedures for recording and reporting Serious Adverse

All serious adverse events will be recorded in the patient notes, CRF and on the sponsor SAE form. The SAE form will be submitted immediately (within 24hrs) to the sponsor on the email address: pharmacovigilance@moorfields.nhs.uk. All SAEs will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. The description of the event must ensure the clinical picture is captured accurately.

All SAEs will be recorded until 30 days after the last injection of Eylea is given.

The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

SUSARs

The Principal Investigator or sub/co-investigator will complete the sponsor's serious adverse event form indicating a SUSAR and the form will be emailed to the sponsor using the following email address: pharmacovigilance@moorfields.nhs.uk immediately (within 24hours) of his / her becoming aware of the event. The Chief or Principal Investigator will respond to any SUSAR queries raised by the sponsor as soon as possible.

11.3.1 Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the injection of Eylea, or an unrelated event. These will be reported up until 12 months post 1st injection of the last patient, or 30 days after the giving of the last injection of Eylea (whichever is the furthest away).

11.3.2 Reporting SUSARs

The sponsor will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

11.3.2.1 Reporting SUSARs in International Trials

N/A

11.3.3 Development Safety Update Reports

The sponsor will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and the Sponsor's office. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended

11.3.4 Annual progress reports

An annual progress report (APR) will be submitted to the REC that gave favourable opinion 12 months after the date on which the favourable opinion was given. The chief investigator will prepare the APR.

11.3.5 Pregnancy (If applicable)

If a patient becomes pregnant at any point during the duration of the trial:

- It will be recorded in both the patient notes, case report form (CRF) and the sponsor will be notified using the sponsor's SOP
- Immediate cessation of further intravitreal injections will take place
- A letter will be written to the GP (with permission from the patient) recommending that the patient be referred to their local obstetrics and gynaecology team for monitoring
- A letter will be written to the GP (with permission from the patient) asking for correspondence about the health and well-being of any child born to a patient that became pregnant during the trial, or within 6 months of their

last intravitreal injection with Eylea. This includes a child born to a woman who was the partner of a male trial patient.
The patient will be asked to attend an exit follow-up review at 12 months, which will involve the same tests to be undertaken as those still remaining in the study.

11.3.6 Overdose

- Injecting the entire volume of the prefilled syringe could result in overdose.
- If an overdose occurs, it will be recorded in both the patient notes, case report form (CRF) and the sponsor notified (placed on the deviation log)
- Patients that receive an overdose of Eylea will be withdrawn from the trial as it will be unknown to what extent the effects on CMT/BCVA are attributable to the increased amount of drug injected
- If a SAE is associated with an overdose, it will be fully described in the SAE report form

11.3.7 Reporting Urgent Safety Measures

If any urgent safety measures are taken the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

11.4 The type and duration of the follow-up of subjects after adverse events.

Subjects who have experienced an adverse drug reaction will continue to be followed-up until 12 months after the 1st IVT.
Adverse events and reactions will be recorded and reported for up to 30 days

following the last injection of Eylea.

Any SUSAR related to Eylea will need to be reported to the Sponsor irrespective of how long after Eylea administration the reaction has occurred.

11.4.1 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach, which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

10 Data management and quality assurance

12.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data.

A trial number will be used for identification on the CRFs. The chief investigator or delegated authorised individual will be responsible for keeping a separate log file which links the study ID and the patient's details will be kept on a password protected computer

12.2 Data Collection Tools and Source Document Identification

The investigator will work with the trial team to maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, results of Vision charts, OCT scans etc.

A subset of the information in the source documents will be determined by the chief investigator and other suitably trained members of the study team to be the trial dataset for the Case Report Forms (CRFs). This will be agreed with the trial statistician, senior data manager and communicated to the R&D IT team. CRFs will be designed and produced by the R&D IT Team according to the sponsor's CRF template. All data will be entered legibly in black ink with a ball-point pen. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialled and dated by the person making the alteration. Overwriting or use of correction fluid will not be permitted.

It will be the responsibility of the investigator to ensure the accuracy of all data recorded on the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling. The completion of CRFs will be signed off by the Chief Investigator or delegated authorised individual (Principal Investigator) as outlined in the delegation log.

All information on CRFs must be traceable to the source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

Methods used to maximise completeness of data include: telephoning subjects who have not attended for their appointment and data collection forms will be included as appendices.

12.3 Data handling and analysis

The completed CRFs will be checked for completion by the research nurse / research manager. The delegated authorised individual will then enter data onto the trial database created by the R&D IT team. Data entry will be carried out within 1 week of CRF completion. When all patients have been recruited, the R & D data officer will double data enter 10 CRFs randomly selected by the senior data manager, plus 100% of primary outcome data for all patients. The first and second data entries will be compared for completion and consistency checks will be performed. The error rate will be calculated and errors will be corrected as necessary. Sense checks, logic checks and range checks will be performed. Data queries will be corrected and data will be cleaned. The database will then be locked and data transferred for analysis by trial statisticians using STATA statistical software. Data management process will follow the trial data management plan and MEH SOPs for data management.

The database will be produced using a file/server system. The front end will use a bespoke Microsoft Visual Studio application and the back end (data storage) will be

Microsoft SQL server. All database development is carried out by the R&D IT team and the database will be validated to GAMP 5 standards.

The back end database is an installation of Microsoft SQL Server. The database is only available within the MEH WAN/Intranet area. All servers are backed up daily and with multiple restore points every day. Backup copies exist in more than one place as tapes are sent securely to another of our sites. There is to be no sending of trial data externally. All MEH clinical trial databases are part of the MEH disaster recovery strategy and have a 5 day Recovery Time Objective.

This is a single-site trial so data will not be transferred to another site. However, if for any reason the data is required for electronic transfer, it will be transferred in accordance with the UK Data Protection Act 1998 as well as MEH Information Security Policy and Trust Information Governance Policy. Documented record of data transfer and measures will be in place for the recovery of original information after transfer.

13 Record keeping and archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. In line with Moorfields Eye Hospital SOP, the retention periods outlined below should be adhered to:

Document	Minimum Retention period	Reference
CTIMP TMF & medical files of trial subjects (UK trial only)	5 years after conclusion of the trial	UK SI 2004/1031 (as amended) 31A (7 and 8) Commission Directive 2005/28/EC
CTIMP TMF & medical files of trial subjects where data is used to support a marketing authorisation	15 years after completion or discontinuation of trial OR for at least 2 years after the granting of the last marketing authorisation in the EEA OR for at least 2 years after formal discontinuation of clinical development of the investigational product.**	Commission Directive 2003/63/EC (amending Directive 2001/83/EC) ICH Guideline for Good Clinical Practice E6 (R1)

The essential documents and trial database will be kept in a locker within the Clinical Research Facility at Moorfields Eye Hospital.

Chief Investigators/Principal Investigators are responsible for the secure archiving of essential trial documents contained within the site file and the trial database as per their trust policy. All essential documents will be retained for a minimum of 5 years after completion of trial including the subject's medical notes.

Destruction of essential documents will require authorisation from the Sponsor.

14 Statistical Considerations

Catey Bunce is the trial statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

14.1 Outcomes

14.1.1 Primary outcomes

Primary Objective:

To report mean Central Macular Thickness (CMT) at 12 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

14.1.2 Secondary outcomes

To report mean Central Macular Thickness (CMT) at 6 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

To report mean change in Central Macular Thickness (CMT) as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months.

To report the mean BCVA ETDRS letter score at 6 and 12 months in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three

loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

To report the mean change in BCVA ETDRS letter score in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months.

To report mean macular volume at 6 and 12 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

To report mean change in macular volume as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months.

To report all AEs and SAEs at any time point during the 12 month study of using intravitreal Eylea in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema.

To report the mean retinal sensitivity at 6 and 12 months using Microperimetry in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

To report the mean change in retinal sensitivity using Microperimetry in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months.

To report the mean number of intravitreal injections administered in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

14.2 Sample size and recruitment

14.2.1 Sample size calculation

This is an exploratory study which aims to assess the safety and efficacy of Eylea in patients with RP and CMO. We have chosen a sample size of 30 patients which is justified on the basis that 30 subjects will provide an estimate of the mean change in CMT from baseline to 12 months with reasonable precision as advocated by Browne (1995) and Hertzog (2008).

14.2.2 Planned recruitment rate

We plan to start recruiting patients from 5th December 2015 for a period of 9 months. This would equate to 3 to 4 patients being recruited per month if a total of 30 patients are required. This figure has been deemed to be attainable in practice.

14.3 Statistical analysis plan

The statistical analysis plan will be written in advance of the data analysis by a trial statistician. All statistical tests will use a two-sided P value of 0.05. All confidence intervals will be 95 % and two sided.

14.3.1 Summary of baseline data and flow of patients

Baseline characteristics will be presented to provide an overview of patient characteristics at baseline. Summary statistics will be presented as mean and standard deviation for continuous (approximate) normally distributed variables, median and interquartile range for non-normally distributed variables and frequency and percentage for categorical variables.

A consort flow chart will be constructed.

14.3.2 Primary outcome analysis

- Mean Central Macular Thickness (CMT) at 12 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol will be estimated with a 95 % confidence interval.

14.3.3 Secondary outcome analysis

Summary statistics for all secondary outcomes will be presented. Where appropriate the standard error and two-sided 95 % confidence interval will also be presented alongside these. For the case of any outcome measures which are presented as a proportion, a 95 % confidence interval will be computed by the exact binomial method.

- To report mean Central Macular Thickness (CMT) at 6 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

- To report the mean change in Central Macular Thickness (CMT) as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months.

- To report the mean BCVA ETDRS letter score at 6 and 12 months in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol.

- To report the mean change in BCVA ETDRS letter score in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months.
- To report mean macular volume at 6 and 12 months as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.
- To report mean change in macular volume as measured with SDOCT in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months.
- To report all AEs and SAEs at any time point during the 12 month study of using intravitreal Eylea in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema.
- To report the mean retinal sensitivity at 6 and 12 months using Microperimetry in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.
- To report the mean change in retinal sensitivity using Microperimetry in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and six months, and baseline and twelve months.

- To report the mean number of intravitreal injections administered in eyes of patients with Retinitis Pigmentosa associated with cystoid macular oedema treated with three loading doses of Eylea at monthly intervals followed by a treat and extend protocol between baseline and twelve months.

14.3.4 Sensitivity and other planned analyses

It is inevitable that some patients will be lost to follow up. If data are missing for any patients, reasons for this may be important and these will be examined and dealt with as appropriate.

A detailed statistical analysis plan will be written by the trial statistician at the beginning of the trail (before any analysis begins) detailing all of the planned baseline, primary, secondary, safety and sensitivity analyses.

14.4 Randomisation methods

Not applicable

14.5 Interim analysis

There are no planned interim analyses.

14.6 Other statistical considerations

Statistical analysis will be done according to the statistical analysis plan. Any deviation(s) from the original statistical analysis plan will be described and justified in the final report.

15 Name of Committees involved in trial

The Trial Management Group (TMG) will oversee recruitment and data management. The trial will also include a Trial Steering Committee (TSC) and a Independent Data Monitoring Commmittee (IDMC).

16 Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

17 Ethics and regulatory requirements

Ethical issues that may arise, include:

- Participants may be approached in a public space

  Patients may be recruited from the medical retina clinics, in which case discussion about the trial will be undertaken in a private cubicle to maintain privacy

- Fear or pain / distress / discomfort to the participant

  A full explanation about intravitreal injections will be given to the patient, both verbally and written down in the patient information sheet. The patient will make an informed decision whether they would like to be involved with the trial or not. Reasons such as fear of having the intravitreal injections would be an understandably valid reason for a patient to choose not to enter the trial. No coercion will occur.

- Issues of confidentiality and privacy, or lack of anonymity

  Patient information kept in the Case Report Forms (CRF) will be anonymised by using only their subject number, hospital number and date of birth. Their name will not appear on this data.

- Security of personal data, retention and disposal of the data

  Clinical Report Forms are kept in a locked filing cabinet, in a locked room. Access to this information is only permitted to those people who are named and involved in the trial.

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before the site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) and be granted written permission. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 11.3.7 for reporting urgent safety measures).

Within 90 days after the end of the trial, the Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with an end of study report of the clinical trial, which will then be submitted to the MHRA and main REC within 1 year after the end of trial declaration has been submitted.

18 Monitoring requirement for the trial

A trial specific monitoring plan will be established for studies as part of the oversight planning. The trial will be monitored in accordance with the agreed plan.

19 Finance

Bayer, the manufacturer of Eylea, will be funding this trial

20 Insurance

MEH participates in the Clinical Negligence Scheme for Trusts (CNST), run by the NHS Litigation Authority, which pools the risk of clinical negligence claims.
NHS indemnity (for negligent harm) will cover MEH employees, both substantive and honorary, who are working in the course of their NHS employment and in respect of conducting research projects which must have received NHS Permission. MEH will not accept liability for any activity that has not been properly registered and Trust approved.

21 Publication policy

All proposed publications will be discussed with Sponsor prior to publishing other than those presented at scientific forums/meetings. Publications and or study report findings will be submitted onto the European clinical trials database in line with current EU guidance.

http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf

22 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

23 References

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