EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/758988/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eylea

International non-proprietary name: AFLIBERCEPT

Procedure No. EMEA/H/C/002392/II/0021

Note

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

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List of abbreviations

ADA	anti-drug antibodies
ADR	adverse drug reaction
AE(s)	adverse event(s)
(w)AMD	(wet) age-related macular degeneration
ANCOVA	analysis of covariance
ATE	arterial thromboembolic event
AUC0-last	Area under the concentration-time curve from time zero to the last validated measurable plasma concentration
BCVA	best corrected visual acuity
BRVO	branch central retinal vein occlusion
CI	confidence interval
Cmax	Maximum observed plasma concentration of the drug
CMH	Cochran-Mantel-Haenszel
CNV	choroidal neovascularization
CrCl	creatinine clearance
CRT	central retinal thickness
CRVO	central retinal vein occlusion
D	diopter
DA	disc areas
DME	diabetic macular edema
ELISA	enzyme-linked immunosorbent assay
ETDRS	Early Treatment Diabetic Retinopathy Study
EQ-5D	EuroQol group quality of life questionnaire – 5 dimensions
FA	fluorescein angiography
FAS	full analysis set
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IOP	Intraocular pressure
IVT	intravitreal
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LS	least squares
mCNV	myopic choroidal neovascularization (i.e CNV secondary to pathologic myopia)
MedDRA	Medical Dictionary for Regulatory Activities
NEI VFQ-25	National Eye Institute 25-item Visual Function Questionnaire
OC	observed case
OCT	optical coherence tomography
(v)PDT	(Visudyne or verteporfin) photodynamic therapy
PI	Product Information
PL	Package Leaflet
PM	Pathologic Myopia
PPS	per protocol set
PRAC	Pharmacovigilance Risk Assessment Committee
PT(s)	Preferred Term(s) according to MedDRA
QoL	quality of life
RMP	Risk Management Plan
RVO	retinal vein occlusion
SAE	serious adverse event
SAF	safety analysis set
SD	standard deviation
SOC	System Organ Class according to MedDRA
TEAE	treatment emergent adverse event
tmax	Time of maximal concentration
VA	Visual acuity
VEGF(R)	vascular endothelial growth factor (receptor)
VTE	VEGF Trap-Eye/aflibercept

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bayer Pharma AG submitted to the European Medicines Agency on 10 March 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include a new indication for adults for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV). As a consequence, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC. Section 6.6 was proposed to be updated to amend the instructions for use including improved pictograms. The Package Leaflet was proposed to be updated in accordance.

In addition, some editorial changes were proposed in the SmPC, in Annex II and in the PL.

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

Information on paediatric requirements

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

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pierre Demolis Co-Rapporteur: Robert James Hemmings

Timetable	Actual dates
Submission date	10 March 2015
Start of procedure:	28 March 2015
CHMP Co-Rapporteur Assessment Report	22 May 2015
CHMP Rapporteur Assessment Report	1 June 2015
PRAC Rapporteur Assessment Report	5 June 2015
PRAC Outcome	11 June 2015
Updated Joint Rapporteurs' Assessment Report	19 June 2015
Request for Supplementary Information	25 June 2015
MAH's responses submitted to the CHMP on:	23 July 2015
Joint rapporteurs' preliminary assessment report on MAH's responses circulated on:	1 September 2015
Joint Rapporteurs' updated assessment report on the MAH's responses circulated on:	17 September 2015
PRAC RMP advice and assessment overview adopted by PRAC	10 September 2015
CHMP opinion:	24 September 2015

2. Scientific discussion

2.1. Introduction

The active substance in Eylea is aflibercept (also referred to as VEGF Trap or VTE), a recombinant fusion protein consisting of ligand binding regions within the extracellular domains of the human vascular endothelial growth factor (VEGF) receptor (VEGFR) linked to the Fc domain of human immunoglobulin IgG1. More specifically, aflibercept comprises immunoglobulin domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the constant region of a human IgG1.

VTE binds multiple isoforms of VEGF-A and placental growth factor-2 which are members of the VEGF family of angiogenic factors that act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells, producing pathological neovascularization, excessive vascular permeability, and vascular inflammation.

Eylea has been approved in the European Union (EU)/European Economic Area through the centralised procedure by Commission Decision on 22 November 2012. The initial indication granted was for the treatment of adult patients with neovascular (wet) age-related macular degeneration (AMD). The indication was later extended by Commission Decision on 26 August 2013, 6 August 2014 and 24 February 2015 to include treatment of adult patients with visual impairment due to macular oedema

secondary to central retinal vein occlusion (CRVO), due to diabetic macular oedema (DME), and secondary to branch retinal vein occlusion (BRVO), respectively.

Eylea is a solution for injection available in vials or pre-filled syringes. The recommended dose is 2 mg aflibercept equivalent to 50 microlitrers given intravitreally (IVT).

Eylea is administered no more frequent than on a monthly basis. For AMD and DME, three and five initial consecutive doses are recommended, respectively. For RVO, initially, three or more consecutive monthly doses may be needed.

Present application

With this application, the MAH proposed to extend the indication for adults to treatment visual impairment due to myopic choroidal neovascularisation (myopic CNV or mCNV), i.e. CNV secondary to pathologic myopia (PM). In this new indication, it is proposed to initiate treatment with a single injection and then, additional injections are given as needed only when there are signs of disease activity. The application is supported by the results of a single Phase III randomized controlled trial, MYRROR, in East-Asian mCNV patients, as well as an evaluation of the ethnical insensitivity of VTE in Asians and Caucasians.

Problem statement

PM or high myopia, defined as refractive error ≥ -6 diopters (D), is a leading cause of blindness as it is associated with myopic retinopathy and other complications. It is the most severe form of myopia that affects 2% of all myopic eyes. Both environmental factors and genetic factors are known to contribute to myopia development.

CNV is one of the most common vision-threatening complications of pathologic myopia, a leading cause of blindness.

CNV is one of the most common vision-threatening complications of PM. In contrast to CNV secondary to neovascular AMD, the socioeconomic impact of visual impairment due to mCNV may be even more devastating as it typically affects young individuals in the working age group (Cohen et al., 1996), and occurs about one decade earlier than other common blinding eye diseases.

Among Caucasians in Australia and the United States, approximately 20% of the population has (simple) myopia while in many Asian countries the incidence exceeds 20%. The incidence of high myopia among Asians has been reported to be around 2.3 times greater than among Caucasians. The prevalence of CNV in individuals with PM was reported to be 5.2%-11.3% with a prevalence of visual impairment due to pathologic myopia ranging from 0.1%-0.5% in European studies and from 0.2%-1.4% in Asian studies. Most eyes progress to 20/200 or worse within 5 to 10 years after onset. During the natural course of mCNV, patients progressively lose VA at a rate of approximately 10 to 15 letters (2 to 3 lines) over 2 years.

The increased prevalence of pathological myopia among Asian adults compared to American and European adults is attributed to a number of factors including urbanization, intensive studying, high educational attainment, lack of outdoor activities, and longer axial length in young individuals. In Japan, pathological myopia is the leading cause of unilateral and bilateral blindness (Iwase et al., 2010). According to some literature reports (Williams KM et al., Ophthalmology 2015) the prevalence of myopia is also increasing in Europe.

Myopia can be classified as simple or pathologic (synonyms: progressive, degenerative). Eyes with simple myopia are elongated proportional to the refractive error (usually 0.3 mm/diopter [D]), but lack pathologic fundus changes, even if the refractive error is high. PM encompasses the condition of the abnormal elongation of the axial length of the eyeball (> 26 mm) associated with high myopia refractive

errors, usually ≥ - 6.0 D, and have, in addition, pathologic tissue alterations such as retinal pigment epithelial thinning and defects, lacquer cracks and Bruch's membrane ruptures, CNV, subretinal haemorrhage, and choroidal thinning and atrophy, which ultimately lead to central macular degeneration and macular scarring.

Morphologically, mCNV appears as a flat, small, grayish subretinal membrane beneath or in close proximity to the fovea. The mechanisms of CNV formation in pathologic myopia are still not fully clarified. Hypoxia in the outer retina due to choroidal stretching and thinning is considered part of the pathological pathway and has been suggested to stimulate VEGF secretion.

The visual prognosis of mCNV patients is generally poor without treatment. Following an early stabilization of vision, visual acuity gradually and progressively decrease over time primarily.

The most common treatment of choice for non-subfoveal CNV lesions is laser photocoagulation. However, it is associated with permanent loss of vision within the treated area, as well as formation of new abnormal vasculature. Photodynamic therapy (PDT) with verteporfin (vPDT) has been used for treating mCNV in the past decade in Europe, the United States, Hong Kong, Singapur, Taiwan and South Korea, but not Japan. The available data suggest that PDT might reduce the risk of visual loss compared to placebo, but no improvement in mean visual acuity was observed. Therefore, maintenance of VA is, at the very best, the expected benefit of treatment with vPDT.

More recently, IVT anti-VEGF agents have been used to treat visual impairment in patients with mCNV. Ranibizumab was approved in the EU by Commission Decision in July 2013. Efficacy of IVT ranibizumab compared to vPDT was established in a phase III, randomized, double-masked, multicenter, active-controlled study. Over 12 months, individualized ranibizumab treatment was effective in improving and sustaining visual acuity and was generally well tolerated in patients with mCNV.

Rational for proposed change

VTE, like ranibizumab, acts by binding and inhibiting VEGF. Patients with active mCNV have elevated levels of VEGF in the aqueous humor of the concerned eye(s). Similar to wet AMD, by inactivating VEGF, VTE is thought to inhibit neovascular growth and associated exudation, with subsequent suppression of CNV growth. Based on previous experience with other anti-VEGF agents in mCNV patients, treatment with VTE is expected to have a direct and immediate clinical effect of visual improvement.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

In line with the Guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00 corr 1), since aflibercept is a protein and unlikely to result in a significant risk to the environment, Eylea is exempted from an environmental risk assessment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Applicant confirmed that the clinical trials were performed in accordance with GCP.

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

- Tabular overview of clinical studies

Study title (number)	Objective	Study design	Treatments	Number of subjects	Duration of treatment	Study status
MYRROR Sponsor's study no: 15170	Efficacy, Safety, and Tolerability of Intravitreal VEGF Trap-Eye in Subjects with Choroidal Neovascularization Secondary to Pathologic Myopia	Phase III multi-centre, randomized, double-masked, sham-controlled	Day 0 to Week 20: 2 treatment groups: - VTE 2 mg: Active injection at Baseline and every 4 weeks if study re-treatment criteria were met. - Sham: Only sham injections. Week 24 to Week 44: Mandatory VTE injection for Sham group at Week 24. Thereafter, all subjects received VTE according to study re-treatment criteria	Total: 122 VTE 2 mg: 91 Sham: 31	24 weeks for the primary endpoint Further treatment as needed until Week 44 (follow-up at Week 48)	Complete to Week 48

2.3.2. Pharmacokinetics

The objective of the clinical pharmacology program for VTE in patients with mCNV was to characterize the pharmacokinetics (PK) and systemic exposure of VTE after IVT administration in patients with mCNV and to compare the PK and the systemic exposure with that observed in patients with neovascular AMD or CRVO.

Sparse samples were collected in all patients enrolled in the clinical Phase III study MYRROR. Additionally,

dense sampling has been performed in a limited sub-group of patients.

Analytical Methods

Free VTE and bound VTE plasma concentrations were measured using validated enzyme-linked immunosorbent assay (ELISA) methods. The assay for bound VTE is calibrated using standards for the complex VEGF:VTE standards and the results are reported for bound VTE as weight per volume of the complex. Therefore, the concentration of the bound complex is to be adjusted by multiplying with a factor of 0.717 to account for the VEGF present in the complex (referred to as adjusted bound VTE). The lower limit of quantitation (LLOQ) for the free and adjusted bound assays is 0.0156 mg/L and 0.0315 mg/L, respectively.

Sample collection, sample handling, and analytical methods were identical to previous PK analyses in other indications, allowing for comparability across programs.

Results

- Dense sampling data

Dense sampling was performed in a sub-set of 8 patients treated with VTE in the MYRROR study. Non-compartmental analysis was only done for patients with concentrations >LLOQ and no more than 2 subsequently missing concentrations. Samples were taken at Baseline (pre-dose) and 4 h, 8 h, 1 d, 2 d, 3 d, 4 d, 7 d, 14 d and 28 d after the first dose.

A plasma concentration-time profile for free VTE valid for non-compartmental analysis was observed in only one subject. In the other 7 subjects, none or maximal 2 plasma samples had free VTE concentrations >LLOQ. However, even these quantifiable concentrations were close to the analytical limits and were no more than about 4-fold higher than the LLOQ (with the exception of one subject where it was 7-fold higher). Cmax could only be calculated for one subject (27.3 µg/L) and was reached after 94.4 hours. The mean concentration-time profile of free VTE over all 8 subjects of the PK sub-study showed concentrations >LLOQ in 1 or 2 subjects per time points from 4 hours to 7 days post-dose. Two weeks after the first administration of VEGF-Trap Eye all plasma concentration values for free VEGF-Trap were <LLOQ.

Exploratory subgroup analyses with respect to age, sex, BMI, creatinine clearance, hepatic impairment, and geographical region was not conducted because nearly all free VEGF Trap plasma concentrations in the samples for the general PK assessment of trough concentrations were below LLOQ.

The mean Cmax of adjusted bound VTE was around 130 µg/L as measured after a single IVT administration of VTE 2 mg. In studies in healthy volunteers with intravenous administrations of up to 4 mg/kg submitted and assessed in a previous application for AMD, mean maximum adjusted bound concentrations of 2000 to 3000 µg/L were found, with bound concentrations showing only minor increases with doses above 2 mg/kg. It was, therefore, assumed that substantial binding of endogenous VEGF is attained at doses of 2 mg/kg and above. The concentrations of bound VTE as measured using dense sampling in MYRROR are, thus, approximately 4% to 7% of those measured in the studies with intravenous VTE. The value of 7% may be regarded as a rough estimate for the maximum endogenous VEGF that was bound under the study conditions. Taking this into account, the present data suggest that only a minor fraction of the available systemic endogenous VEGF is expected to be bound to VTE.

- Sparse sampling data

Blood samples for the general PK assessment (sparse sampling schedule) of systemic trough concentrations of free and bound VTE were collected before dose administration at Weeks 0, 4, 12, 24, 36, and at any time at Week 48 from all (91) patients in MYRROR.

IVT administration of VTE 2 mg resulted in pre-dose plasma concentrations (after repeated

administrations) of free VTE that were below the LLOQ for the vast majority of subjects. Mean trough concentrations of free VTE were only measurable in a few patients, mainly at the Day 1, 1-4h post-dose time point. This result was expected because VTE is absorbed slowly from the eye into the systemic circulation, where it binds to endogenous VEGF.

Mean trough concentrations of adjusted bound VTE were 104 µg/L at Week 4 and declined until Week 48 to 39.3 µg/L. All individual patients (from the mandatory sparse sampling PK assessment of trough concentrations and the PK sub-study) had adjusted bound VTE plasma concentrations <331 µg/L at all time points. Exploratory sub-group analysis of adjusted bound VTE suggested higher systemic distribution of VTE in Japanese patients (63.1±83.1 µg/L) compared to non-Japanese patients (15.8±41.0 µg/L). Further investigation by the MAH in response to a CHMP request showed that the increase in Japanese patients at week 24 was not present at week 12. Considering the variability and scarcity of the data the finding at week 24 was considered to be likely an artefact. The sub-group analyses did not reveal any clinically relevant differences.

Repeated administration of VTE 2 mg every 4 weeks did not result in any accumulation of the compound in plasma. Therefore, the PK results suggest no increased risk of systemic side effects with longer treatment duration.

- Comparison of data across studies:

Analytical techniques and sampling schedule in mCNV (MYRROR Study), CRVO (GALILEO Study), and neovascular AMD (VGFT-OD-0702.PK and VIEW 2) were similar, thus eliciting a reliable inter-study comparison.

While small numerical differences were observed between in the PK parameters, the data did not suggest a meaningful difference in systemic exposure following a 2 mg IVT administration of VTE in patients with mCNV compared with patients with neovascular AMD or CRVO. The arithmetic mean Cmax values for free VTE in mCNV, CRVO, and AMD patients were low, and were only approximately 1 to 3 times the LLOQ (15.6 µg/L) of the assay. Notable, as previously mentioned, the Cmax value for free VTE after single administration in mCNV was based on only one evaluable subject.

2.3.3. Pharmacodynamics

The pharmacodynamics (PD) of VTE were discussed as part of the initial approved marketing application for treatment of subjects with wAMD. See also section 2.1. for a summary of the mode of action.

Anti-drug antibody (ADA) information was collected in the MYRROR study from all subjects. A total of 4 samples from 2 subjects (both in the VTE 2 mg group) had positive responses in the ADA assay. Both subjects exhibited positive assay results at Baseline. One of them had a Baseline titer level of 240, a Week 24 titer level of 480 and a Week 48 titer level of 120. Since the post-treatment titer levels did not increase more than 4-fold over Baseline levels, the assay results in this subject were attributed to pre-treatment immunoreactivity. The other subject had a Baseline titer level of 30 (the assay minimal titer) and was negative at the Week 24 and 48 time points, suggesting the subject was negative for ADA. None of the samples demonstrated neutralizing activity.

Mean systolic blood pressure and mean diastolic blood pressure varied only slightly during the course of the study compared to baseline values.

2.3.4. Discussion on clinical pharmacology

The analytical techniques used for PK sampling in the mCNV study were the same as those previously used and assessed for other indications.

Based on dense sampling in a small subgroup of 8 subjects in MYRROR with a single dose of 2 mg VTE, generally low free VTE plasma concentrations were observed. As expected, most of the VTE in the systemic circulation is bound to the endogenous VEGF. Additional data from sparse sampling showed no accumulation of free or adjusted bound VTE after repeated administration. Exploratory sub-group analysis of adjusted bound VTE suggested higher systemic distribution of bound VTE in Japanese patients compared to non-Japanese patients at Week 24. However, this finding was considered to be likely an artefact as no increase was observed at week 12 and in light of the small samples size and high variability of the data.

Cross study comparison revealed no marked differences in systemic exposure between patients groups (mCNV, AMD and CRVO). However, some of the PK parameters were estimated from small patient numbers of patients, thus limiting the interpretability.

ADA assays resulted only in few positive samples, which were not treatment-emergent, exhibited low titers, and did not demonstrated any neutralizing activity. There was also no effect on mean blood pressure associated with increased blood pressure after IVT administration in the Asian population tested in the MYRROR study.

Generally, the CHMP was of the view that the effects of Eylea in non-Japanese patients should be evaluated based on clinical efficacy and safety data. Of note, the impact of the ethnic intrinsic factor on the PK profile of IVT VTE administration is summarised in section 2.4.

2.3.5. Conclusions on clinical pharmacology

Taking into account all available data, neither the difference in study population demographics, nor difference in disease-related pathology resulted in any clinically meaningful difference in the systemic exposure to free or bound forms of VTE in the mCNV subjects as compared to wAMD or CRVO subjects previously studied. No signs of immunogenicity or blood pressure increases were observed. Overall, the CHMP was of the opinion that the data provided were sufficient to support the application for Eylea for an extension of the indication in the treatment of adults with visual impairment due to mCNV.

2.4. Clinical efficacy

The clinical development program of Eylea for the treatment of mCNV consisted of a single phase III study (MYRROR) conducted in 20 centers in Japan (15), Hong Kong (1), Singapore (1), South Korea (1) and Taiwan (2). The MYRROR Phase III trial aimed at investigating if VTE will improve visual acuity (VA) in subjects with choroidal neovascularization secondary to pathologic myopia and whether there will be other potential advantages, such as prevention of moderate vision loss, associated with the use of VTE.

2.4.1. Dose response study(ies)

No dedicated dose response studies were carried out by the MAH.

The rationale for the final dose selection of 2 mg IVT injections of VTE was based on the safety and efficacy results from the phase III clinical trials conducted for AMD and CRVO. No new data were generated specifically for mCNV.

The dosing regimen in the MYRROR study was chosen based on expert advice as well as publicly available data from studies of other anti-VEGF agents, which suggested that single IVT administration of an anti-VEGF drug was sufficient to cause CNV blockade (disappearance of leakage in fluorescein angiography) and visual improvement in the majority of tested patients with mCNV (Hayashi et al., Am J Opthalmol.

2009). Besides, no significant difference was seen in the improvement of visual acuity achieved with initial 3-monthly doses followed by additional dosing, and a single dose followed by additional dosing (Wakabayashi et al., Retina 2011). Thus, subjects in the MYRROR study were treated with a dose of 2 mg VTE administered by a single injection at study start (or at Week 24 for the control group, which had only sham treatment through week 20) and followed by additional doses in case of persisting or recurring disease, based on pre-defined re-treatment criteria (see Section 2.4.2. for details).

At the time of starting the MYRROR study, no anti-VEGF therapy had been approved in this indication anywhere in the world. However, some peer-reviewed publications of previous non-controlled studies suggested that anti-VEGF may become the new standard therapy in the treatment of CNV secondary to pathologic myopia. However, confirmation of this assumption by appropriate studies was still missing. In some Asian countries (Hong Kong, Singapore, Taiwan, and South Korea) vPDT was approved in the treatment of CNV secondary to pathologic myopia but not in Japan, where most of the study sites for MYRROR were planned. Therefore, Sham was selected as control in MYRROR.

2.4.2. Main study

MYRROR: Phase-3, Multi-center, Randomized, Double-masked, Sham-controlled Study of the Efficacy, Safety, and Tolerability of Intravitreal VEGF Trap-Eye in Subjects with Choroidal Neovascularization Secondary to Pathologic Myopia

Methods

Study participants

Subjects eligible for this study were adult males and females with active mCNV as defined by leakage on fluorescein angiography (FA), and with a best corrected visual acuity (BCVA) of 73 to 35 letters (ETDRS equivalent of 20/40 to 20/200). A Central Reading Centre confirmed the eligibility of a subject. Based on the medical judgment of the investigator, the subject's decrease in vision was primarily the result of current active mCNV.

Only one eye was designated as the study eye. However, safety of the fellow eye was monitored also, and all systemic adverse events (AEs) were collected. For subjects who met eligibility criteria in both eyes, the eye with the worst VA was selected as the study eye. If both eyes had equal VA, the eye with the clearest lens and ocular media and least amount of subfoveal scarring or chorioretinal atrophy was selected. If there was no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology, and subject preference was considered in making the selection.

The main inclusion and exclusion criteria are summarised below.

Main inclusion criteria:

1. Men and women ≥ 18 years of age.
2. Myopia ≥-6 diopter or axial length ≥ 26.5 mm.
3. Active subfoveal or juxtafoveal CNV secondary to PM as defined by leakage on FA.
4. BCVA of 73 to 35 letters (ETDRS equivalent of 20/40 to 20/200) in the study eye at 4 meters.
5. Decrease in vision in the study eye was determined by the investigator, using his/her medical judgment, to be primarily the result of the current active mCNV

Main exclusion criteria:

Ophthalmic criteria

1. Only one functional eye.
2. Ocular media of insufficient quality to obtain fundus and optical coherence tomography (OCT) images in the study eye
3. Greatest linear dimension of the lesion in the study eye was >12 disc areas (DA)
4. Recurrent mCNV in the study eye
5. Aphakia in the study eye
6. History or presence of CNV with an origin other than PM in the study eye (with a particular attention to exclude an origin of DME or diabetic retinopathy (DR), AMD, or polypoidal choroidal vasculopathy).
7. Ocular inflammation (including trace or above) or external ocular inflammation in the study eye.
8. Concurrent disease in the study eye that would compromise BCVA or require medical or surgical intervention during the study period.
9. Any ocular disorder in the study eye that, in the opinion of the investigator, may have confounded the interpretation of the study results.
10. Significant scarring or atrophy in the fovea that indicated substantial irreversible vision loss in the study eye.
11. History of idiopathic or autoimmune-associated uveitis in either eye.
12. Evidence at examination of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye or current treatment for serious systemic infection.
13. Vitreomacular traction or traction retinal detachment, epiretinal membrane in either eye as evident biomicroscopically or on OCT that was considered by the investigator to have a significantly effect on central vision.
14. Any iris neovascularization and/or vitreous haemorrhage in either eye 15.
15. Uncontrolled glaucoma (i.e. intraocular pressure (IOP) ≥ 25 mm Hg on optimal medical regimen, or previous filtration surgery in either eye).
16. Prior and concomitant treatments in the study eye:
    - Any prior or concomitant treatment with another investigational agent for mCNV.
    - Any previous panretinal photocoagulation or subfoveal thermal laser therapy.
    - Any prior treatment with PDT.
    - Cataract surgery within 3 months prior to Day 1.
    - Yttrium-aluminum-garnet laser capsulotomy within 2 months prior to Day 1.
    - Any other intraocular surgery within 3 months prior to Day 1.
    - History of vitreoretinal surgery and/or scleral buckle surgery.
17. Any prior treatment with anti-VEGF agents in either eye, or systemic use of an anti-VEGF product at any time.
18. Previous use of intraocular or periocular corticosteroids in either eye within 3 months prior to Day 1.

Other criteria

19. Previous assignment to treatment during this study
20. Uncontrolled hypertension defined as a single measurement of systolic blood pressure > 180 mm Hg, two consecutive measurements of systolic blood pressure ;> 160 mm Hg, or diastolic blood pressure > 100 mm Hg on optimal medical regimen.
21. History of cerebrovascular disease or myocardial infarction within 6 months prior to Baseline/Day 1.
22. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contra-indicated the use of an investigational drug, may have affected interpretation of the results of the study, or render the subject at high risk from treatment complications.
23. Renal failure requiring dialysis or renal transplant.
24. Known serious allergy to the fluorescein sodium for injection in angiography
25. Inability to obtain fundus photographs or fluorescein angiograms of sufficient quality.

Treatments

Eligible subjects were enrolled into the study and randomly assigned to one of two treatment groups, active or Sham.

VTE: Patients randomized to the VTE group received an IVT injection of 2 mg VTE at Visit 2 (Day 1). Additional active injections were allowed in subjects who, upon assessment, met one or more of the study re-treatment criteria, up to and including Week 44.

Sham+VTE: Patients randomized to the control group (Sham) were to receive Sham injections every 4 weeks from Visit 2 (Day 1) to Visit 7 (Week 20). Patients underwent assessment for re-treatment criteria (in order to maintain masking) but did not receive VTE injections regardless of the outcome of this assessment. At Week 24, subjects were assessed against the study re-treatment criteria (in order to maintain masking). They received a mandatory active injection with VTE 2 mg regardless of the outcome of the re-treatment assessment. They then received VTE 2 mg injections in the study eye, if protocol re-treatment criteria were fulfilled until Week 44.

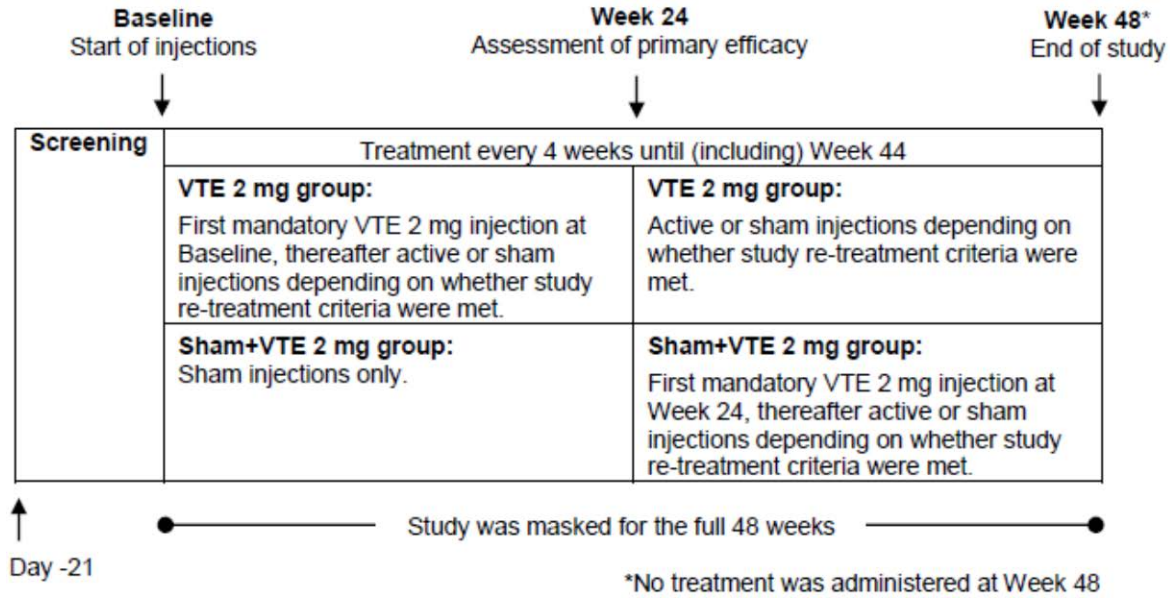


Figure 1 – Study design

Subjects who received therapy with another investigational agent to treat mCNV or any other condition were excluded from the study. If the fellow eye had mCNV, this eye was allowed to receive any approved treatment (i.e., not investigational treatment) other than the study drug, other anti-VEGF therapies, or steroids. The fellow eye was not considered an additional study eye.

Retreatment were at maximum every 4 weeks. At all visits when the re-treatment criteria were not met, the subject received a Sham injection in order to maintain masking.

Re-treatment criteria:

Retreatment criteria aimed at determining recurrence or persistence of mCNV.

At least one of the following criteria was to be met for re-treatment with VTE:

- Reduction in VA by ≥5 letters from the previous ETDRS examination.
- CRT increases by more than 50 ìm from the time of the previous examination.
- New or persistent cystic retinal changes, subretinal fluid, or pigment epithelial detachment.

- New or persistent CNV or bleeding.
- As deemed necessary by the investigator based on his/her clinical impression and/or diagnostics performed in the context of standard medical care.

Objectives

Primary objective: To assess the efficacy of intravitreal (IVT) administration of VTE in comparison to Sham treatment on the mean change in BCVA from baseline to Week 24 in patients with CNV secondary to pathologic myopia (myopic CNV).

Secondary objectives:

- To assess the safety and tolerability of IVT administration of VTE in subjects with mCNV.
- To assess the efficacy of IVT administration of VTE on vision related quality of life (QoL) as assessed using the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25).
- To assess changes in leakage at the CNV site as seen on FA.
- To describe the systemic exposure to study drug by PK investigations.

Outcomes / endpoints

Primary Efficacy Variable: Mean change from Baseline in BCVA as measured by ETDRS at Week 24.

Secondary Efficacy Variable: Proportion of subjects who gained ≥15 letters in BCVA at Weeks 24.

Additional Efficacy Variables:

- Mean change from baseline in BCVA as measured by ETDRS at each visit and at Week 48.
- Vision gains and losses ≥ 5, 10, or 15 letters at each visit and at Week 24 and 48.
- Change in central retinal thickness (CRT) (µm) from Baseline at Weeks 24 and 48.
- Change in CNV lesion size (DA) from Baseline at Weeks 24 and 48.
- Change in area of leakage (DA) from Baseline at Weeks 24 and 48.
- Change in total NEI-VFQ-25 score from baseline at Weeks 24 and 48.
- Change in EQ-5D score from baseline at Weeks 24 and 48.
- Proportion of subjects who withdrew from study drug by Week 24 and Week 48.
- Ad hoc analysis of exposure: Number of injections administered in total and per quarter of treatment period (i.e., within Weeks 0 to 8, Weeks 12 to 20, Weeks 24 to 32, and Weeks 36 to 44).

The assessment of BCVA was performed by site personnel who have been trained and certified for assessment using the ETDRS chart by a qualified training centre. OCT images were read locally by site personnel who have been trained and certified by the Central Reading Centre. The results of FA and fundus photography (FP) were evaluated centrally by the Central Reading Centre.

Sample size

One hundred-twenty subjects (90 active and 30 Sham) were planned to be randomized. The assumptions made in the calculation of the sample size were based on the following:

- The difference between treatment groups in the changes in BCVA from Baseline to Week 24 will be 10 letters.
- The changes in BCVA from Baseline will be normally distributed with a common standard deviation of 14 letters.
- A t-test with a one-sided alpha level of 0.025 will be used to demonstrate statistical significance.

Based on these assumptions, 112 evaluable subjects in total were calculated to provide 90% power to show statistical significance for the primary endpoint. To be conservative, i.e. estimating that 5% of the randomized subjects will not be eligible for the primary analysis, 120 subjects were to be randomized from all participating study sites.

Randomisation

Subjects eligible for the study were randomly assigned in a 3:1 ratio to either the VTE or control (Sham-injection) group. Randomization was stratified by country. Assignment into a treatment group was done using an Interactive Voice Response System or an Interactive Web Response System.

Blinding (masking)

All study-site personnel (except for those performing designated unmasked roles) remained masked to treatment assignment of all subjects in order to ensure an unbiased assessment of VA, safety, and ancillary study measures. An independent monitor responsible for pharmacy site visits was unmasked to study treatment. Patients, all other study personnel, and Steering Committee members remained masked to treatment assignment.

At all visits patients were assessed for re-treatment criteria and received either active of Sham injections in order to maintain masking. In the active arm, even when the re-treatment criteria were not met, the subject received a Sham injection; in the Sham arm, even when the re-treatment criteria were met, the subject received a Sham injection until 24 Week.

The masked principal investigator was responsible to assess AEs, perform the masked assessment of efficacy, and assess re-treatment criteria at Visits 3 through 13. Other masked study site personnel performed the masked assessments of VA, FA and fundus photography, and OCT, as well as other non-ophthalmic assessments.

Statistical methods

Populations for analysis

The full analysis set (FAS) included all randomized subjects who received any study drug and have a Baseline and at least one post-baseline BCVA assessment. The FAS will be analysed as randomized.

The per protocol set (PPS) included all subjects in the FAS who attended at least two scheduled visits during the first 24 weeks of the study, with the exception of those subjects who are excluded because of major protocol violations, where the violation is one that may affect the interpretation of study results (e.g., missing two consecutive injections). The PPS also included subjects who were deemed to be treatment failures at any time during the first 24 weeks of the study. The PPS will be analysed as treated.

The safety analysis set (SAF) included all subjects who received any study drug. The safety analysis set was analysed as treated.

Statistical methods

The primary efficacy analysis compared the change in BCVA from Baseline to Week 24 between treatment groups by calculating a two-sided 95%-confidence interval (CI) of the between-group treatment difference using an analysis of covariance (ANCOVA) model, including "treatment group" and "country" as fixed effects and "baseline BCVA" as covariate. If the lower limit of the 95% CI was greater than 0, then superiority of VTE to Sham injection was established. This superiority testing was conducted with the FAS.

Additional analysis of the primary endpoint was also performed on the PPS to support the FAS.

A last observation carried forward (LOCF) approach for the primary analysis and an observed case analysis (OC) for both the FAS and the PPS as sensitivity analysis were chosen at first. However, during the actual study conduct, several dropouts were recorded. Therefore, to further explore the robustness of the pre-specified primary analysis and assess the impact of missing data on the efficacy evaluation more comprehensively, further sensitivity analyses were added before database lock and unmasking of the study data including multiple imputation analysis of missing values and a mixed model for repeated measurements. Additional sensitivity analysis of the confirmatory secondary efficacy variable were also introduced. This analysis used worst case imputation, i.e., subjects prematurely discontinuing treatment before Week 24 were considered as failures for this analysis.

During the period from baseline to W24, all other visual and anatomic criteria were analysed as exploratory including CRT. All efficacy and safety analyses performed at Week 48 were similar to the analyses performed at Week 24 and all considered exploratory. The difference between treatment groups and a corresponding two-sided 95% CI was estimated for a descriptive purpose.

The continuous variables, including the mean change from baseline to Week 48 in BCVA, CRT, CNV lesion size, EQ-5D score, NEI VFQ-25 total score and leakage measured by FA, were assessed using an ANCOVA model, including treatment groups and country (country designations) as fixed effects and Baseline measurement as a covariate.

The categorical variables, including the proportion of subjects who gained/lost ≥ 5, 10, or 15 letters and who were withdrawn by Week 48, were analyzed using the Cochran-Mantel-Haenszel (CMH) method, weight-adjusted for country (country designations), from which the difference in proportions of subjects between treatment groups and a corresponding two-sided 95% confidence interval were estimated.

Subgroups

All subgroup analyses, except the by-country analysis were for descriptive purposes only. These variables are summarized below:

- Country (Japan, Other): statistical tests repeated for Japanese subjects
- Sex (Male, Female)
- Age group (<45, 45-<55, 55-<65, 65-<75, ≥75)
- Baseline BCVA > 20/200 (letters read ≥ 35) and BCVA ≤ 20/200 (letters read ≤ 34)
- Duration of disease (< 2 months, ≥ 2 months)
- Renal impairment, classified by creatinine clearance (CrCl) at baseline (Normal: CrCl > 80 mL/min, Mild: 50 < CrCl ≤ 80 mL/min, Moderate: 30 < CrCl ≤ 50 mL/min, o Severe: CrCl ≤ 30 mL/min or requiring dialysis)
- Hepatic impairment (Yes, No)

In the VEGF Trap-Eye group, the descriptive summary of efficacy variables was also calculated by number of active injections.

Results

Participant flow

A total of 173 subjects were screened and 122 subjects (70.5%) were randomized. Of the 51 subjects (29.5%) not randomized, most (n= 49 or 28.3%) were considered to be screening failures, 2 (1.2%) withdrew their consent.

Table 1 – Subject disposition (all enrolled subjects)

Disposition	VTE 2mg	Sham	Total
Number of subjects			173
Enrolled			173
Screening failures / non-randomized			51
Randomized	91 (100.0%)	31 (100.0%)	122 (100.0%)
Study drug never administered	0	0	0
Treated	91 (100.0%)	31 (100.0%)	122 (100.0%)
Not completed 24 weeks treatment	7 (7.7%)	6 (19.4%)	13 (10.7%)
Completed 24 weeks treatment	84 (92.3%)	25 (80.6%)	109 (89.3%)

Among the 122 randomized subjects, 83 (91.2%) subjects in the VTE 2 mg group and 25 (80.6%) in the Sham group, completed the first 24 weeks of study treatment. Patients who discontinued treatment before Week 24 were 8 (8.8%) in the VTE 2 mg group and 6 (19.4%) in the Sham group. Between Week 24 and Week 48, treatment was discontinued in 5 subjects (5.5%) and 1 subject (3.2%) in the Sham+VTE group.

Table 2 - Disposition of Subjects at 24 and 48 weeks in MYRROR Study and Reasons for Premature Discontinuation (All patients All randomized subjects)

	VTE 2 mg N=91	Sham+VTE N=31	Total N=122
Subjects screened; n	---	---	173
Subjects randomized; n (%)	91 (100.0)	31 (100.0)	122 (100.0)
Subjects treated; n (%)	91 (100.0)	31 (100.0)	122 (100.0)
Completed 24 weeks treatment; n (%) [a]	83 (91.2)	25 (80.6)	108 (88.5)
Discontinued treatment before Week 24; n (%)	8 (8.8)	6 (19.4)	14 (11.5)
Primary reason; n (%):			
Adverse event	3 (3.3)	2 (6.5)	5 (4.1)
Withdrawal by subject	3 (3.3)	1 (3.2)	4 (3.3)
Protocol violation	2 (2.2)	0 (0.0)	2 (1.6)
Treatment failure	0 (0.0)	1 (3.2)	1 (0.8)
Switching to other therapy	0 (0.0)	2 (6.5)	2 (1.6)
Completed 48 weeks treatment; n (%) [a]	78 (85.7)	24 (77.4)	102 (83.6)
Discontinued treatment before Week 48; n (%)	5 (5.5)	1 (3.2)	6 (4.9)
Primary reason; n (%):			
Adverse event	2 (2.2)	0 (0.0)	2 (1.6)
Withdrawal by subject	3 (3.3)	1 (3.2)	4 (3.3)
Completed study; n (%) [b]	85 (93.4)	31 (100.0)	116 (95.1)
Not completed study; n (%)	6 (6.6)	0 (0.0)	6 (4.9)
Primary reason; n (%):			
Adverse event	1 (1.1)	0 (0.0)	1 (0.8)
Withdrawal by subject	5 (5.5)	0 (0.0)	5 (4.1)

Note: Percentages are based on all randomized subjects.
a: First and second study period are reported separately (ie, no cumulative description). "Week 24-completer" completed the first 24 weeks of study treatment and received the planned injection (active or sham) at Visit 8 (Week 24). "Week 48-completer" completed treatment up to Week 44.
b: Subjects who remained under study observation until the follow-up visit at Week 48.

During the 24 weeks of the study, in the FAS, the mean of compliance value was 97.41% and 88.71%, in the VTE 2 mg group and the Sham group, respectively. A total of 95.6% of patients in VTE 2 mg group and 83.9% in the Sham group received 80% to 100% of all scheduled treatments.

Recruitment

The MYRROR study was conducted in approximately 20 study sites, in Japan (15), in South Korea (1), in Singapore (1), in Taiwan (2), in Hong Kong (1). The first subject's first informed consent was on 17 December 2010 and last subject's last visit was on 15 August 2013.

Conduct of the study

The original protocol of MYRROR Study is dated 16 September 2010. There were 2 global amendments (dated 8 Mar 2011 and 30 Nov 2011) and 1 local in Japan (dated 23 May 2012).

Amendment no 1 clarified the inclusion criteria.

- Loss of vision in the study eye: The original protocol stated that the onset of symptoms of mCNV (i.e. vision loss in the study eye) must not have occurred earlier than 6 months prior to the signing of the informed consent form (i.e., Screening/Visit 1). This stipulation was removed and replaced with the instructions that the investigator, based on his/her medical judgment, would

determine if the loss of vision in the study eye was primarily the result of the current active mCNV.

- The specifics of the subject's myopia (i.e., ≥-6 Diopter with axial length ≥ 26.5 mm) was modified to state that eligible subjects would have myopia ≥ -6D OR axial length ≥ 26.5 mm.
- Juxtafoveal lesions was defined as those within 1 to 199 ìm of the center of the fovea. The criterion was further clarified to state that if exact location of the lesion could not be determined by the study site, the Central Reading Center would be responsible to classify the lesion as subfoveal or juxtafoveal.
- The ECG should be performed before (after was removed and replaced) study drug injection or PK sample collection.

It was clarified that the reference to China included both China mainland and Hong Kong (see below).

Amendment no 2 was made to allow partial collection of pharmacokinetic samples from subjects who were unable to perform all visits required for the PK sub-study. Furthermore, the total sample size was reduced because no Clinical Trial Permit to conduct the study in the People's Republic of China could be obtained.

Amendment no 3 allowed part of the subjects in Japan to begin a participation in the PK sub-study at Visit 8/Week 24.

Baseline data

Demographic and Baseline disease characteristics are summarised in Table 3 and Table 4.

Table 3 – Demographic Characteristics of All Study Subjects in MYRROR (FAS)

	VTE 2 mg N=90 (100%)	Sham N=31 (100%)	Total N=121 (100%)
Sex; n (%)			
Male	25 (27.8%)	4 (12.9%)	29 (24.0%)
Female	65 (72.2%)	27 (87.1%)	92 (76.0%)
Age; years			
Mean (SD)	58.5 (13.7)	57.5 (12.1)	58.2 (13.3)
Median	62.0	59.0	62.0
Min - Max	27-83	27-82	27-83
Race; n (%)			
Asian	90 (100.0%)	31 (100.0%)	121 (100.0%)
Weight; kg			
Mean (SD)	58.20 (11.6)	57.28 (10.18)	57.96 (11.22)
Median	56.95	57.00	57.00
Min - Max	37.0 – 101.0	42.5 – 91.0	37.0 – 101.0
Height; cm			
Mean (SD)	159.11 (8.55)	157.17 (7.80)	158.61 (8.38)
Median	158.95	157.00	158.00
Min - Max	142.0 – 181.0	142.0 – 181.0	142.0 - 181.0
Body mass index; kg/m^2			
Mean (SD)	22.91 (3.69)	23.12 (3.18)	22.96 (3.55)
Median	22.70	22.98	22.87
Min - Max	17.1 – 36.2	18.1 – 31.2	17.1 – 36.2
Country; n (%)			
Japan	67 (74.4%)	23 (74.2%)	90 (74.4%)
Korea	9 (10.0%)	3 (9.7%)	12 (9.9%)
Singapore	2 (2.2%)	0	2 (1.7%)
Taiwan	7 (7.8%)	3 (9.7%)	10 (8.3%)
Hong Kong	5 (5.6%)	2 (6.5%)	7 (5.8%)

The majority of subjects were female (n=92; 76.0%), all were Asian (n=121; 100%) with about 74% Japanese. The total population ranged in age from 27 to 83 years (mean 58.2 +/-13.3 years).

Table 4 - Baseline Disease Characteristics of the Study Eye in MYRROR (FAS)

	VTE 2 mg N=90	Sham+VTE N=31	Total N=121
Baseline BCVA letter scores; n (%)			
> 20/200 (≥ 35 letters)	87 (96.7)	31 (100.0)	118 (97.5)
≤ 20/200 (≤ 34 letters)	3 (3.3)	0	3 (2.5)
Mean ± SD	56.4 ± 9.8	56.6 ± 8.9	56.5 ± 9.5
Median	58.0	59.0	59.0
Min - Max	28-76	37-70	28-76
Baseline CRT by OCT; microns			
Mean ± SD	349.7 ± 91.3	354.2 ± 107.2	350.9 ± 95.2
Median	343.0	365.0	346.0
Min - Max	147-777	125-674	125-777
Baseline IOP (mmHg)			
Mean ± SD	15.2 ± 2.7	15.8 ± 2.8	15.4 ± 2.7
Median	15.0	16.0	16.0
Min - Max	8-22	11-24	8-24
Time since myopic CNV diagnosis; n (%)			
≥ 2 months	17 (18.9)	7 (22.6)	24 (19.8)
< 2 months	73 (81.1)	24 (77.4)	97 (80.2)
Baseline CNV lesion size (DA)			
Mean	0.4086	0.3334	0.3894
SD	0.5028	0.3413	0.4666
Median	0.2535	0.2450	0.2480
Minimum	0.008	0.018	0.008
Maximum	2.758	1.851	2.758

BCVA=Best corrected visual acuity, DA=Disc area, OCT=Optical coherence tomography, SD=standard deviation

In both groups, the majority of subjects had a disease duration of < 2 months (the mean duration of disease was about 5 months). Most subjects had a Baseline BCVA of ≥20/200 (≥35 letters); the mean baseline BCVA letter score was approximately 56.5 letters. The mean baseline CRT was about 350 microns.

All but one subject in the Sham group had a classic CNV type of lesion diagnosed at screening. The location of CNV was central (subfoveal) in the majority of subjects of the two groups. Some numerical differences in the mean CNV lesion size were noted (0.4086 ± 0.5028 DA in the VTE 2 mg group versus 0.3334 ± 0.3413 DA in the Sham+VTE 2 mg group, whereas medians were similar with 0.2535 DA and 0.2450 DA, respectively).

Baseline axial length was similar with 28.79 mm (SD 1.52) in the VTE 2 mg group and 28.61 mm (SD 1.70) in the Sham group. The majority of subjects in both treatment groups (>97% in each group) had a leakage present.

Baseline vital signs in MYRROR Study were balanced across groups (SAF).

The most common ocular medical and surgical history findings in the study eye were choroidal neovascularization (all subjects, 100.0%), pathologic myopia (120 subjects, 98.4%), cataract (24 subjects, 19.7%), and cataract operation (24 subjects, 19.7%).

Table 5 - Most common (at least 2 subjects in either group) ocular medical history findings in the study eye by MedDRA PT (SAF)

Preferred Term (MedDRA Version 16.0)	VTE 2 mg (N=91) n (%)	Sham+VTE (N=31) n (%)	Total (N=122) n (%)
Subjects with at least one finding	91 (100.0)	31 (100.0)	122 (100.0)
Choroidal neovascularisation	91 (100.0)	31 (100.0)	122 (100.0)
Pathologic myopia	89 (97.8)	31 (100.0)	120 (98.4)
Cataract	22 (24.2)	2 (6.5)	24 (19.7)
Cataract operation	18 (19.8)	6 (19.4)	24 (19.7)
Dry eye	10 (11.0)	2 (6.5)	12 (9.8)
Intraocular lens implant	5 (5.5)	4 (12.9)	9 (7.4)
Cataract cortical	6 (6.6)	2 (6.5)	8 (6.6)
Conjunctivitis allergic	6 (6.6)	0 (0.0)	6 (4.9)
Myopia	5 (5.5)	0 (0.0)	5 (4.1)
Cataract nuclear	3 (3.3)	1 (3.2)	4 (3.3)
Glaucoma	2 (2.2)	2 (6.5)	4 (3.3)
Asthenopia	2 (2.2)	1 (3.2)	3 (2.5)
Retinal degeneration	3 (3.3)	0 (0.0)	3 (2.5)
Retinal haemorrhage	3 (3.3)	0 (0.0)	3 (2.5)
Retinal tear	3 (3.3)	0 (0.0)	3 (2.5)
Cataract subcapsular	2 (2.2)	0 (0.0)	2 (1.6)
Ocular hypertension	2 (2.2)	0 (0.0)	2 (1.6)

The most frequent non-ocular medical history findings were in the MedDRA SOCs Vascular Disorders with the PT hypertension in 27.9% overall (31.9% in the VTE 2 mg group and 16.1% in the Sham group). There was a somewhat higher proportion of subjects in the VTE 2 mg group than in the Sham group with medical/surgical history findings reported for the SOCs Metabolism and Nutrition Disorders (20.9% vs. 9.7%), Psychiatric Disorders (13.2% vs. 6.5%), Respiratory, Thoracic and Mediastinal Disorders (9.9% vs. 3.2%), Immune System Disorders (8.8% vs. 3.2%), and Gastrointestinal Disorders (13.2% vs. 6.5%). Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps) were more frequent in the Sham group with 9.7% vs. 4.4% in the VTE 2 mg group. Differences ≥ 5% in the occurrence of effects (PTs) which were more frequent in the VTE 2 mg group included insomnia (9.9% vs. none in the Sham group), allergic rhinitis with 5.5% and no subject in the Sham group, hyperlipidemia (8.8% in the VTE 2 mg group, 3.2% in the Sham group).

The most commonly used concomitant medications were in the classes 'Ophthalmologicals' (91 [100%] VTE group, 30 [96.8%] Sham group) and 'Cardiovascular system' (49 [53.8%] VTE 2 mg; 12 [38.7%] Sham+VTE 2 mg with calcium channel blockers [24.6% overall], serum lipid reducing agents [21.3% overall], and agents acting on the renin angiotensin system [18.0% overall]).

Numbers analysed

All of the 122 randomized subjects (91 in the VTE 2 mg group and 31 in the Sham group) received at least one study treatment (i.e., VTE or Sham injection).

Table 6 – Overview of analyses sets (all randomised patients)

	VTE 2 mg N=91 n (%)	Sham+VTE N=31 n (%)	Total N=122 n (%)
Subjects randomized [a]	91 (100.0)	31 (100.0)	122 (100.0)
Subjects valid for SAF	91 (100.0)	31 (100.0)	122 (100.0)
Subjects valid for FAS	90 (98.9)	31 (100.0)	121 (99.2)
Subjects valid for PPS	86 (94.5)	29 (93.5)	115 (94.3)
Subjects valid for PKS	91 (100.0)	25 (80.6) [b]	116 (95.1)
Excluded from SAF	0 (0.0)	0 (0.0)	0 (0.0)
Excluded from FAS	1 (1.1)	0 (0.0)	1 (0.8)
Excluded from PPS	5 (5.5)	2 (6.5)	7 (5.7)
Excluded from PKS	0 (0.0)	6 (19.4) [c]	6 (4.9)

a: The analysis set for anti-drug antibodies (ADA) testing consisted of all 122 randomized subjects for whom serum samples were taken pre-dose at Baseline and at Week 48.
b: All 25 subjects in the sham group who switched to active treatment from Week 24 onwards.
c: These 6 subjects were not analyzed for PK, since they never received active VTE (discontinued treatment before Week 24).

A total of 7 (5.7%) subjects had major protocol deviations [5 (5.5%) in the VTE 2 mg group and 2 (6.5%) in the Sham group]. The most common major protocol deviation was inclusion/exclusion criterion not met, which occurred with 4 subjects in total (3 subjects in the VTE 2 mg group and one subject in the Sham+VTE 2 mg group).

A total of 22 subjects (15 subjects in the VTE 2 mg group and 7 subjects in the Sham+VTE 2 mg group) were involved in any events of unmasking. In the Sham+VTE 2 mg group, one subject required premature emergency unmasking because of a non-ocular, non-serious AE 'impetigo contagiosa'.

Outcomes and estimation

Results of the MYRROR Study are presented for both 24 and 48 weeks.

Exposure/Number of injections

Treatment Compliance and Number of Injections at Week 24:

Table 7 - Subjects by number of active injections and study period through Week 48 (FAS)

	VTE 2 mg (N=90) n (%)	Sham+VTE (N=31) n (%)	Total (N=121) n (%)
No. of active injections from Baseline to Week 20 [a]			
1	19 (21.1)	0 (0.0)	19 (15.7)
2	25 (27.8)	0 (0.0)	25 (20.7)
3	22 (24.4)	0 (0.0)	22 (18.2)
4	7 (7.8)	0 (0.0)	7 (5.8)
5	4 (4.4)	0 (0.0)	4 (3.3)
6	13 (14.4)	0 (0.0)	13 (10.7)
No. of active injections from Week 24 to Week 44 [b]			
missing (none)	40 (44.4)	6 (19.4)	46 (38.0)
1	22 (24.4)	2 (6.5)	24 (19.8)
2	14 (15.6)	6 (19.4)	20 (16.5)
3	3 (3.3)	6 (19.4)	9 (7.4)
4	2 (2.2)	2 (6.5)	4 (3.3)
5	3 (3.3)	0 (0.0)	3 (2.5)
6	6 (6.7)	9 (29.0)	15 (12.4)
Total no. of active injections from Baseline to Week 44			
missing (none)	0 (0.0)	6 (19.4)	6 (5.0)
1	13 (14.4)	2 (6.5)	15 (12.4)
2	14 (15.6)	6 (19.4)	20 (16.5)
3	26 (28.9)	6 (19.4)	32 (26.4)
4	11 (12.2)	2 (6.5)	13 (10.7)
5	3 (3.3)	0 (0.0)	3 (2.5)
6	5 (5.6)	9 (29.0)	14 (11.6)
7	3 (3.3)	0 (0.0)	3 (2.5)
8	5 (5.6)	0 (0.0)	5 (4.1)
9	3 (3.3)	0 (0.0)	3 (2.5)
11	1 (1.1)	0 (0.0)	1 (0.8)
12	6 (6.7)	0 (0.0)	6 (5.0)
All active injections by category			
missing (none)	0 (0.0)	6 (19.4)	6 (5.0)
>3	37 (41.1)	11 (35.5)	48 (39.7)
1 to 3	53 (58.9)	14 (45.2)	67 (55.4)
4 to 6	19 (21.1)	11 (35.5)	30 (24.8)
7 to 9	11 (12.2)	0 (0.0)	11 (9.1)
10 to 12	7 (7.8)	0 (0.0)	7 (5.8)

Max=Maximum, Min=Minimum, SD=Standard deviation

a: Excluding the active injections at Week 24; information taken from MYRROR 24-week CSR No. PH-37295.

b: Including the active injections administered at Week 24. Six subjects in the Sham+VTE 2 mg group discontinued study treatment before Week 24 and thus were not exposed to any active injections.

Regarding the number of active injections for the VTE group, in the first part of the study, from Baseline to Week 20, 73.3% of patients in the VTE group needed ≤ 3 active injections. This was reflected by the median number of active injections (3 injections) and the mean number of active injections (2.9 injections) for the overall VTE population. In the second period of the study, the mean number of active injections decreased to less than 1.5 injections in the VTE group (median=1 injection). The mean number of active injections applied to the Sham+VTE group in the second period of the study was slightly higher than the number applied to the VTE group from Baseline to Week 24 (3.9 vs 3) with a median of 3 injections.

The mean interval between injections in subjects who had received at least 2 injections was 37.1 days in the Sham+VTE 2 mg group versus 46.5 days in the VTE 2 mg group whereas the mean interval between first and second injection was 47.2 days in the Sham+VTE 2 mg group versus 54.1 days in the VTE 2 mg group.

Data were also analyzed by quarters of the treatment length (ie, Baseline to Week 8, Weeks 12 to 20, Weeks 24 to 32, and Weeks 36 to 44). According to this analysis, most of the injections were administered in the first quarter of the study, with less frequent re-injections over the subsequent 3 quarters.

The maximum number of active injections in the VTE 2 mg group was 12 through the 48 weeks period of treatment and 6 in the Sham+VTE group through the same period. Six subjects in the VTE group (6.7%) received 12 injections, while 13 subjects (14.4%) were treated with only 1 injection during the entire study period (FAS). In the Sham+VTE 2 mg group, 6 subjects (19.4%%) were not exposed as they had discontinued study treatment before Week 24, 2 subjects (6.5%) had received 1 injection, and 9 subjects (29.0%) had received the maximum number of 6 active injections (FAS).

The reasons for retreatment were mainly 'new or persistent CNV or bleeding', and 'deemed necessary by the investigator'. A total of 96.7% of subjects who fulfilled retreatment criteria also received an active VTE injection.

- Primary Efficacy Variable: Change in BCVA Score from Baseline until Week 24

Mean BCVA at Baseline was comparable in the VTE group and in the Sham group. At Week 24, the mean change from Baseline in the VTE group was 12.1 letters and -2.0 letters in the Sham group.

Using the ANCOVA model, after adjusting country effect and Baseline BCVA measurement, the difference between treatment groups in Least Square (LS) mean changes from baseline to Week 24 was 14.1 ETDRS letters, with a 95% CI of 10.8-17.4 and a p-value < 0.0001.

Table 8 - Change in BCVA letter score from Baseline until Week 24, ANCOVA (FAS, LOCF)

	VTE 2 mg [a] N=90	Sham N=31
Mean BCVA (SD) at Baseline	56.4 (9.8)	56.6 (8.9)
Mean BCVA (SD) at Week 24	68.5 (10.8)	54.6 (9.8)
Mean change from Baseline to Week 24	12.1	-2.0
LS mean change	13.2	-0.9
Difference in LS mean changes [b]	14.1	
95%-confidence interval [b]	[10.8; 17.4]	
p-value [b]	<0.0001	

BCVA=Best corrected visual acuity, ETDRS=Early Treatment Diabetic Retinopathy Study, LS=least squares, SD=Standard deviation

[a] VTE 2 mg administered at Baseline and potentially every 4 weeks in case of disease recurrence

[b] Point estimate, 95% CI and p-value are based on treatment difference (VTE 2 mg-Sham) in LS mean changes, using an analysis of covariance (ANCOVA) model with treatment group and country (country designations) as fixed effects. Baseline value of BCVA was included in the model.

The results when reproduced in the PPS showed a very similar trend.

Sensitivity analyses (OC, Mixed Model for Repeated Measurements and Multiple Imputation) were consistent with the primary analysis.

Results in subgroups (country, sex, age groups, Baseline BCVA score, duration of target disease, renal impairment, hepatic impairment, number of active injections and antibody status) were all favouring the VTE groups over the Sham groups and were consistent for the FAS and PPS. In the VTE subjects receiving 1, 2, 3 and > 3 active injections, the mean changes from Baseline in BCVA were 11.8 letters (n=19), 14.4 letters (n=25), 13.8 letters (n=22) and 8.3 letters (n=24), respectively.

The mean change from Baseline at Week 24 in BCVA score in Japanese was compared to non-Japanese. Using the LOCF approach (FAS), in the VTE 2 mg group, the mean change in BCVA from Baseline at Week 24, was 10.9 letters vs 15.6 letters, in Japanese (n=67) and non-Japanese Asian subjects (n=23), respectively. In the Sham group, the mean change in BCVA from Baseline at Week 24, was -3.7 letters versus 2.8 letters in Japanese (n=23) and in non-Japanese subjects (n=8), respectively. Using the ANCOVA model with baseline BCVA measurement adjustment (LOCF, FAS), difference between treatment groups in LS mean changes from baseline to Week 24 was 14.8 letters (95% CI [10.8-18.8], p-value < 0.0001) and 11.8 letters (95% CI [5.8-17.9], p-value=0.0004) for Japanese and non-Japanese Asian subjects, respectively. This differences was primarily driven by one single subject in the sham group of the non-Japanese group who was withdrawn from study treatment due to a serious adverse event but subsequently treated with 2 injections of ranibizumab leading to a gain of 10 letters of BCVA at Week 24. LOCF analysis excluding this patient from the sham group result in BCVA gains at a similar level for Japanese and non-Japanese Asians (14.8 versus 13.2).

Results for Week 48 and over time

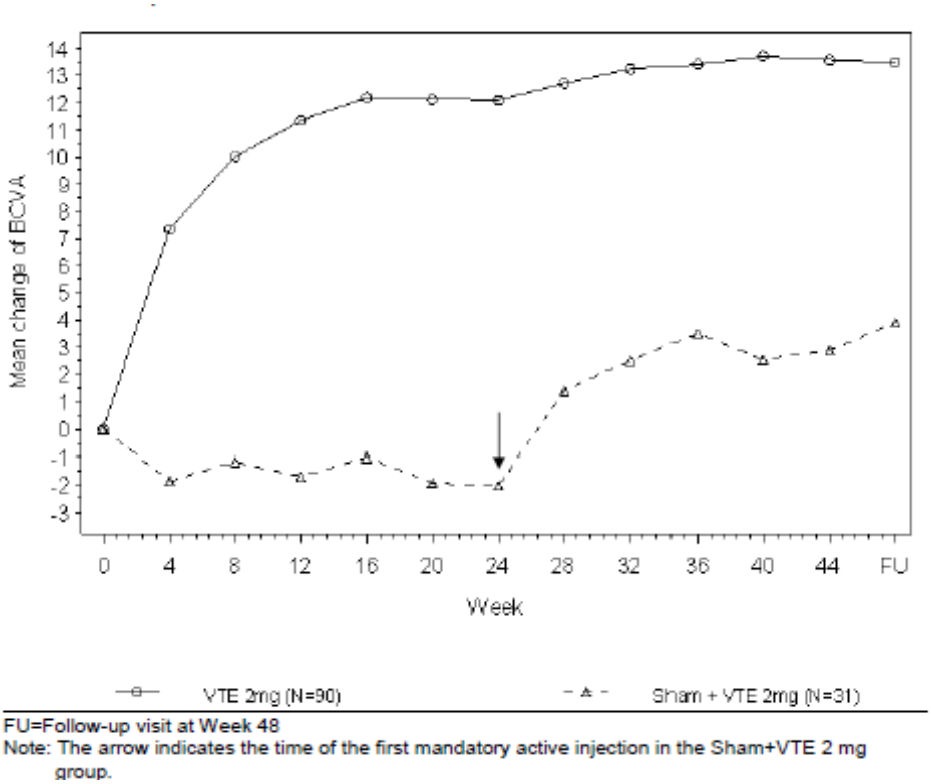
The mean changes in BCVA score at Week 48 compared to Baseline (FAS, LOCF) were 13.5 letters and 3.9 letters in the VTE 2 mg group and Sham+VTE 2 mg group, respectively. The between-group difference of 9.5 letters (LS mean) was statistically significant (p<0.0001).

Mean changes at Week 48 when compared to the Week 24 results (time point corresponding to the 'active treatment Baseline' for the Sham patients who completed the primary endpoint assessment at Week 24) were 1.4 letters and 7.9 letters in the VTE 2 mg group (N=83) and Sham+VTE 2 mg group (N=25), respectively. The improvement in the Sham+VTE 2 mg group from Week 24 to Week 48 was not as marked as previously observed in the VTE 2 mg group from Baseline to Week 24.

Sensitivity analyses (OC) showed a similar trend as FAS, LOCF.

When analysing data by dosing subgroups, the mean BCVA changes from Baseline in the VTE subjects for 1, 2, 3 and >3 injections were 16.7; 15; 14.5 and 11.1 letters gain respectively. In a post-hoc analysis, in the VTE 2 mg group, results were as follows for patients receiving 1-3 active injections: 15.2 ± 8.0 letters, 4-6 active injections: 13.8 ± 8.8 letters, 7-9 active injections: 10.3 ± 10.9 letters, and 10-12 active injections: 4.9 ± 5.8 letters. Therefore with a higher number of injections, gains in VA were more limited similarly to what was observed at Week 24.

With regards to changes in BCVA over time, in the VTE group, the mean change in BCVA from Baseline increased as early as Week 4 (+ 7.4 letters) compared to a mean change of -1.9 letters in the Sham group (see Figure 2).



FU=Follow-up visit at Week 48
Note: The arrow indicates the time of the first mandatory active injection in the Sham+VTE 2 mg group.

Figure 2 - Mean change from Baseline through Week 48 in BCVA (FAS, LOCF)

- Secondary Efficacy Variable: Proportion of patients with ≥15 letter gain in BCVA from Baseline until Week 24

An overview of categorical changes in BCVA over time is provided in Table 9. At Week 24, the proportion of VTE 2 mg subjects who had gained at least 15 letters in BCVA was 38.9% (35/90) whereas in the Sham group, this proportion was clearly lower with 9.7% (3/31). After weight-adjusting by country using two sided Cochran-Mantel-Haenszel method, the difference between treatment groups was 29.2% in favour of VTE with a 95% CI of 14.4%-44.0% and a p-value of 0.0001.

Sensitivity analyses (OC, worst case imputation) were consistent with the FAS, LOCF analysis.

- Exploratory Efficacy Variables:

Mean change from baseline in BCVA as measured by ETDRS at each visit and at Week 48

Results are summarised with the primary variable (see above).

Vision gains and losses ≥ 5, 10, or 15 letters at each visit and at Week 24 and 48

During the first 24 weeks, a rapid increase in the percentage of patients gaining at least 15 letter in BCVA was observed in the VTE group as early as Week 4 and Week 8 (see Figure 3). Thereafter, the percentage of letter gains progressed slowly (from 32.2% at Week 12, to 38.9% at Week 24). A similar tendency was also observed for the gains of at least 10 or 5 letters (see Table 9).

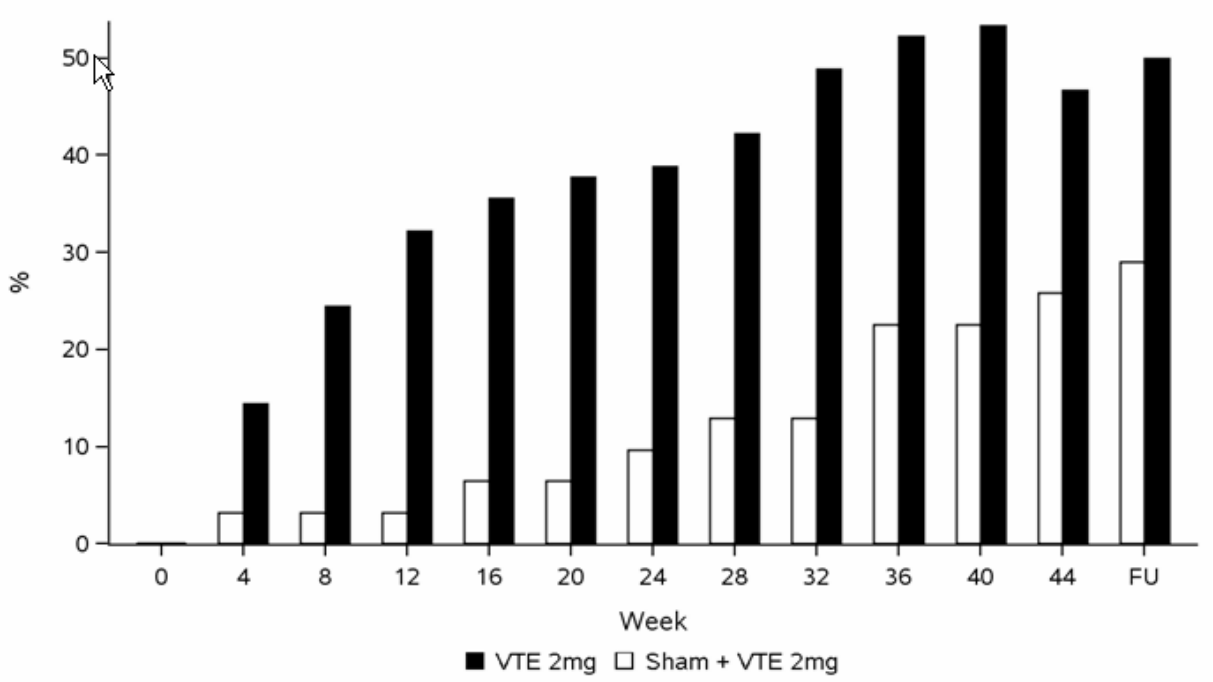


Figure 3 – Proportion of Subjects who Gained ≥15 Letters in BCVA by Study Visit through Week 48 (FAS, LOCF)

Table 9 – Overview of Proportion of Subjects with BCVA Gains/Loss of ≥5, ≥10, or ≥15 ETDRS Letters over Time through Week 24 (FAS)

	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Letter gains; n (%)						
≥ 15 letters						
VTE 2 mg	13 (14.4)	22 (24.4)	29 (32.2)	32 (35.6)	34 (37.8)	35 (38.9)
Sham	1 (3.2)	1 (3.2)	1 (3.2)	2 (6.5)	2 (6.5)	3 (9.7)
≥ 10 letters						
VTE 2 mg	34 (37.8)	52 (57.8)	58 (64.4)	58 (64.4)	60 (66.7)	57 (63.3)
Sham	3 (9.7)	3 (9.7)	4 (12.9)	4 (12.9)	3 (9.7)	4 (12.9)
≥ 5 letters						
VTE 2 mg	61 (67.8)	68 (75.6)	77 (85.6)	76 (84.4)	75 (83.3)	75 (83.3)
Sham	4 (12.9)	4 (12.9)	9 (29.0)	7 (22.6)	8 (25.8)	6 (19.4)
Loss of letters; n (%)						
≥ 5 letters						
VTE 2 mg	4 (4.4)	2 (2.2)	3 (3.3)	2 (2.2)	5 (5.6)	3 (3.3)
Sham	10 (32.3)	8 (25.8)	11 (35.5)	12 (38.7)	10 (32.3)	11 (35.5)
≥ 10 letters						
VTE 2 mg	3 (3.3)	0	1 (1.1)	0	0	0
Sham	6 (19.4)	6 (19.4)	5 (16.1)	4 (12.9)	7 (22.6)	8 (25.8)
≥ 15 letters						
VTE 2 mg	1 (1.1)	0	0	0	0	0
Sham	2 (6.5)	2 (6.5)	4 (12.9)	3 (9.7)	4 (12.9)	2 (6.5)

At Week 48, the differences in the proportion of subjects who gained ≥15 letters still favoured VTE (50%) over Sham+VTE (29%), with a CMH-adjusted difference of 21.0%; 95% CI [1.9; 40.1] (p=0.0308). This was not replicated when using the FAS, OC analysis (difference of 50% in the VTE group versus 37.5% in the Sham+VTE group, with a CMH-adjusted difference of 13.1%; 95% CI [-9.4; 35.6], (p=0.2541). These results again reflecting the improvement of the Sham+VTE group from Week 24 with the initiation of the VTE active treatment. Similar results at Week 48 were obtained for the proportion of subjects who gained either ≥10 or ≥5 letters.

Vision losses remained very limited in the VTE groups compared to the Sham groups. Deterioration by ≥15, ≥10 or ≥5 letters occurred only sporadically in the VTE 2 mg group, while such events were consistently more frequent in the Sham+VTE 2 mg group with a trend to decrease after Week 24.

By Week 48, nominally significant differences were found in the FAS, LOCF analyses for ≥5 (p=0.0012) and ≥10 letter (p=0.035) losers, but not for ≥15 letter losers (p=0.2446). Using the OC analysis no significant differences between groups were seen in either score loss (≥15 letters, p=0.4975; ≥10 letters, p=0.1002; ≥5 letters, p=0.1014).

Change in central retinal thickness (CRT) (µm) from Baseline at Weeks 24 and 48

The results in CRT reduction for Week 24 are summarised in Table 10.

Table 10 – Change from Baseline in CRT (µm) at Week 24 (FAS, LOCF)

	n	Baseline[a] Mean	End point[a] Mean	Mean Change[a]	LS Mean Change	Difference[b] (95% CI)	p-value[c]
VTE 2mg (N= 90)	90	349.7	270.6	-79.1	-85.7		
Sham (N= 31)	31	354.2	350.0	-4.2	-7.8		
VTE 2mg - Sham						-77.9 (-108.9,-46.9)	<0.0001

Abbreviations: CI= confidence interval; FAS= full analysis set, LOCF= last observation carried forward; LS = least squares; n= number of subjects included in analysis; N= number of subjects in treatment group, SD= standard deviation; VEGF Trap-Eye (VTE) 2 mg administered at baseline and potentially every 4 weeks in case of disease reoccurrence

a: absolute values

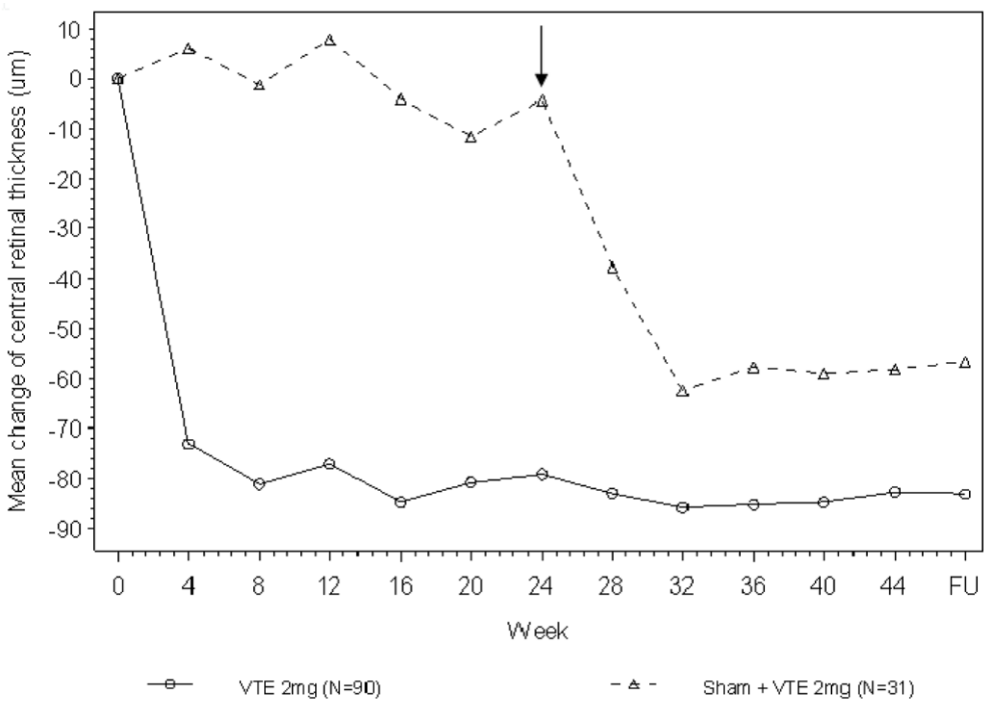
b: Difference in LS mean change. Point estimate and 95% CI are based on treatment difference (VTE 2 mg minus sham) in LS mean changes using an ANCOVA model with treatment group, country, and baseline BCVA category as fixed factors.

c: p-value is based on treatment difference (VTE 2 mg minus sham) in LS mean changes using the model described above.

The difference in CRT reduction between the VTE and Sham groups at Week 24 favoured active treatment (p<0.0001). Using the OC analysis, similarly, results favoured the VTE group. The difference between treatment groups was -67.7 µm; 95% CI [-94.3, -41.1], p <0001.

The VTE group showed a rapid reduction in CRT beginning at Weeks 4 and 8 post-Baseline, which stabilized through Week 24 (see Figure 4). At Week 48, subjects in the VTE group maintained their improvement in CRT (-83.1µm) whereas in the Sham+VTE group, with the initiation at Week 24 of the VTE active treatment, an improvement in CRT was observed, mainly perceptible between Week 24 and Week 32 (-56.7 ± 119.0 µm from Baseline). The between-group difference at Week 48 was -29.3 µm (p=0.0650, LOCF).

The results of the analyses of Japanese subjects using the LOCF method were similar to those for the entire study population.



FU=Follow-up visit at Week 48
Note: The arrow indicates the time of the first mandatory active injection in the Sham+VTE 2 mg group.

Figure 4 - Mean Change from Baseline in CRT (µm) by Visit through Week 48 (FAS, LOCF)

Change in CNV lesion size (DA) from Baseline at Weeks 24 and 48

The Baseline CNV lesion size was lower in the Sham group (0.3401 DA vs 0.4346 DA). Using ANCOVA to adjust for country and Baseline values, the difference observed at Week 24 in CNV lesion size between treatment groups was significantly in favour of VTE (see Table 11). Using the FAS, OC analysis results displayed a similar trend with a difference between treatment groups of -0.50 DA, 95% CI [-0.63, -0.37], p<0.0001.

By Week 48, the LOCF analysis for the (smaller compared to Week 24) adjusted treatment difference of -0.1346 DA still showed a nominally significant difference between treatment groups, while the analysis of observed cases did not.

Table 11 – Mean Change in CNV Lesion Size (DA) from Baseline at Week 24

	n	Baseline[a] Mean	End point[a] Mean	Mean Change[a]	LS Mean Change	Difference[b] (95% CI)	p-value[c]
VTE 2mg (N= 90)	82	0.4346	0.2112	-0.2233	-0.2215		
Sham (N= 31)	30	0.3401	0.6408	0.3007	0.2593		
VTE 2mg - Sham						-0.4808 (-0.5990, -0.3626)	<0.0001

Abbreviations: CI= confidence interval; CNV = choroidal neovascularization; FAS= full analysis set, LOCF= last observation carried forward; LS mean = Least squares mean; n= number of subjects included in analysis; N= number of subjects in treatment group, SD= standard deviation; VEGF Trap- Eye (VTE) 2 mg administered at baseline and potentially every 4 weeks in case of disease reoccurrence
a: absolute values
b: Difference in LS mean change. Point estimate and 95% CI are based on treatment difference (VTE 2 mg minus sham) in LS mean changes using an ANCOVA model with treatment group, country, and baseline BCVA category as fixed factors.
c: p-value is based on treatment difference (VTE 2 mg minus sham) in LS mean changes using the model described above

Change in area of leakage (DA) from Baseline at Weeks 24 and 48

Using an ANCOVA model, after adjusting country effect and Baseline values, the difference observed between treatment groups in area of leakage at Week 24 was significantly in favour of VTE. The FAS OC results displayed a similar trend with a treatment difference of -0.647 DA, 95% CI [-0.803,-0.492], p <0001. The between-group difference diminished, but remained statistically significant by Week 48 for both the LOCF and the OC analyses.

Table 12 - Mean Change in Area of Leakage (DA) from Baseline at Week 24

	n	Baseline[a] Mean	End point[a] Mean	Mean Change[a]	LS Mean Chang	Difference[b] (95% CI)	p-value[c]
VTE 2mg (N= 90)	82	0.7424	0.2681	-0.4743	-0.4792		
Sham (N= 31)	30	0.7063	0.9157	0.2094	0.1856		
VTE 2mg - Sham						-0.6648 (-0.8056,-0.5239)	<0.0001

LOCF = Last observation carried forward
LS mean = Least squares mean; 95% CI = 95% Confidence Interval
a: absolute values
b: Difference in LS mean change. Point estimate and 95% CI are based on treatment difference (VTE 2 mg minus sham) in LS mean changes using an ANCOVA model with treatment group and country as fixed factors.
c: p-value is based on treatment difference (VTE 2 mg minus sham) in LS mean changes using the model described above.

Change in total NEI-VFQ-25 and EQ-5D score from Baseline at Weeks 24 and 48

The National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) was used to assess the efficacy of IVT administration of VTE on vision related quality of life (QoL) [NEI VFQ-25 total score assessed bilateral functional vision and range from 0 (worse possible state) to 100 (best possible state)].

The total NEI-VFQ-25 mean score showed a slight increase from Baseline at Week 24 in the VTE group and a slight decrease in the Sham group (see Table 13). The difference between treatment groups was 5.21 points (LOCF), favouring VTE, p=0.0104. This was not replicated for the OC analysis with a difference of 2.92 points, p=0.1610. Similar results were obtained for Week 48.

Table 13 - Change from Baseline in the NEI VFQ-25 Questionnaire Total Score at Week 24 (FAS, LOCF)

	n	Baseline[a] Mean	Endpoint[a] Mean	Mean Change[a]	LS Mean Change	Difference[b] (95% CI)	p-value[c]
VTE 2mg (N=90)	89	70.72	73.86	3.14	3.45		
Sham (N= 31)	31	72.73	70.14	-2.58	-1.76		
VTE 2mg - Sham						5.21 (1.25, 9.18)	0.0104

Abbreviations: CI= confidence interval; FAS= full analysis set, LOCF= last observation carried forward; n= number of subjects included in analysis; N= number of subjects in treatment group; NEI VFQ-25= National Eye Institute Visual Functioning Questionnaire-25, SD= standard deviation; VEGF Trap-Eye (VTE) 2 mg administered at baseline and potentially every 4 weeks in case of disease reoccurrence
a: absolute values
b: Difference in LS mean change. Point estimate and 95% CI are based on treatment difference (VTE 2 mg minus sham) in LS mean changes using an ANCOVA model with treatment group and country as fixed factors, baseline value is included in the model.
c: p-value is based on treatment difference (VTE 2 mg minus sham) in LS mean changes using the model described above.

The EQ-5D questionnaire was used to assess the overall health status of the subject.

At Week 24, as shown in Table 14, after adjusting the Baseline values, the comparison of mean change of EQ-5D score between groups did not show any significant difference either in the LOCF or OC analysis (difference between groups: -0.0020, 95% CI [-0.0607, 0.0566], p=0.9451). At Week 48, the mean change from Baseline was 0.0154 score points in the VTE group and -0.0252 in the Sham+VTE group. The adjusted treatment difference between groups was 0.0517 score points (95%-CI: [0.0022; 0.1011], p=0.0408 in the LOCF analysis and 0.0583 score points (95%-CI: [0.0025; 0.11142], p=0.0409 in the OC analysis, showing in contrast to Week 24, a significant difference between treatment groups.

Table 14 - Change from Baseline in the EQ-5D Questionnaire Score at Weeks 24 (FAS, LOCF)

	n	Absolute[a] Mean	SD	Mean Change[a]	LS Mean Change	Difference[b] (95% CI)	p-value[c]
VTE 2mg(N= 90)	88	0.8918	0.9104	0.0187	0.0107		
Sham(N= 31)	31	0.8767	0.9108	0.0341	0.0152		
VTE 2mg - Sham						-0.0045 (-0.0579, 0.0490)	0.8690

Abbreviations: CI= confidence interval; EQ-5D= European Quality of Life Questionnaire with 5 dimensions; FAS= full analysis set, LOCF= last observation carried forward; LS = least squares;
n= number of subjects included in analysis; N= number of subjects in treatment group, SD= standard deviation; VEGF Trap-Eye (VTE) 2 mg administered at baseline and potentially every 4 weeks in case of disease reoccurrence
a: absolute values
b: Difference in LS mean change. Point estimate and 95% CI are based on treatment difference (VTE 2 mg minus sham) in LS mean changes using an ANCOVA model with treatment group and country as fixed factors, baseline value is included in the model.
c: p-value is based on treatment difference (VTE 2 mg minus sham) in LS mean changes using the model described above.

Proportion of subjects who withdrew from study drug by Week 24 and Week 48

Through Week 24, a total of 13 subjects discontinued study treatment including 7 (7.7%) in the VTE group and 6 (19.4%) in the Sham group: Six subjects with efficacy data after Baseline of each treatment group (6.7% in VTE group vs. 19.4% in Sham group) were included in this analysis. One subject in the VTE group who dropped out after the first injection but without any post-baseline BCVA measurement was not considered. A 2-sided CMH test adjusted by country showed no statistically significant difference between the two groups (p=0.1012).

The withdrawal rate through Week 48 in the FAS was 13.3% in the VTE group (12 subjects) versus 22.6% in the Sham+VTE group (7 subjects). The CMH adjusted difference between treatment groups was not statistically significant (p=0.2747).

Summary of main study

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15 – Summary of Efficacy for MYRROR

Title: A Phase-3, Multi-center, Randomized, Double-masked, Sham-controlled Study of the Efficacy, Safety, and Tolerability of Intravitreal VEGF Trap-Eye in Subjects with Choroidal Neovascularization Secondary to Pathologic Myopia			
Study identifier	Sponsor's study no: 15170		
Design	Randomized, Double-masked, Sham-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks (primary assessment at Week 24) Screening: 21 days 24 weeks
Hypothesis	Superiority		
Treatments groups	VTE 2mg		One injection of VTE 2mg at Baseline, thereafter monthly active or sham as needed (based on study re-treatment criteria) until Week 44, 91 patients randomized
	Sham		Sham injection at Baseline and every month until Week 20, thereafter one injection of VTE 2mg at Week 24 followed by monthly active or sham as needed (based on study re-treatment criteria) up to Week 44, 31 patients randomized
Endpoints and definitions	Primary endpoint	BCVA change	Change from Baseline in BCVA as measured by ETDRS at Week 24
	Secondary endpoint	BCVA ≥15 responders	Proportion of subjects who gained ≥15 letters compared to Baseline at Week 24
	Exploratory endpoint	CRT change	Change from Baseline in CRT, as assessed by OCT, at Week 24
Database lock	Last subject's last visit: 15 August 2013		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS): all randomized subjects who received any study drug and have a baseline and at least one post-baseline BCVA assessment. Primary analysis: Week 24		
Descriptive statistics and estimate variability	**Treatment group**	**VTE 2mg**	**Sham**
	Number of subject	**90**	**31**
	BCVA change (LS mean)	13.2	-0.9
	BCVA ≥15 responders (%)	35 (38.9%)	3 (9.7%)
	CRT change (mean change µm)	-79.1	-4.2
Effect estimate per	Primary	Comparison groups	VTE 2mg versus Sham

comparison	endpoint: BCVA change	Difference LS mean change	14.1
		95% CI	10.8; 17.4
		P-value	<0.0001
	Secondary endpoint: BCVA ≥15 responders	Comparison groups	VTE 2mg versus Sham
		Difference %	29.2
		95% CI	14.4; 44.0
		P-value	0.0001
	Exploratory endpoint: CRT change	Comparison groups	VTE 2mg versus Sham
		Difference	-77.9
		95% CI	-108.9; -46.9
		P-value	<0.0001
Notes	NA		

Clinical studies in special populations

The development program for Eylea in mCNV was based on one pivotal trial (MYRROR) that, owing to the high prevalence of mCNV in subjects of Asian race, was conducted exclusively in East-Asian countries (Japan, Hong Kong, Republic of Korea, Singapore, and Taiwan). Therefore, the Applicant has conducted an evaluation of the ethnical insensitivity of VTE in Asians and Whites including intrinsic factors and extrinsic factors in line with International Conference on Harmonization ICH E5 guidance, in order to justify extrapolation of data from MYRROR to other ethnicities and geographic regions, in particular European patients.

For the main analysis of ethnical insensitivity, clinical trials conducted with VTE in other approved indications were considered. Statistical evaluation of comparisons included descriptive statistics and regression analyses. The main efficacy results used for comparison were based on the assessment of BCVA and CRT improvements.

The data pooling of the bridging report included 1104 subjects. Among them, the majority were Caucasian (884, i.e. 80%) including 536 AMD, 156 CRVO and 385 DME patients (see Table 16).

Table 16 – Sample Size of Asians and Whites by Indication / Study and Treatment Group

Figures denote number (percentage [a]) of subjects as randomized
Analysis restricted to Asian subjects living in Asia and White ("White") subjects living in Europe

Study	Treatment group	Asian		White [b]		Total	
Wet AMD VIEW 2	Ranibizumab 0.5 mg	32		150		182	
	VTE 2Q4 and 2Q8 combined	69		312		381	
	Subtotal	101	(17.9%)	462	(82.1%)	563	(100%)
CRVO GALILEO	Sham	15		44		59	
	VTE 2Q4	26		71		97	
	Subtotal	41	(26.3%)	115	(73.7%)	156	(100%)
DME VIVID DME	Laser	25		103		128	
	VTE 2Q4 and 2Q8 combined	53		204		257	
	Subtotal	78	(20.3%)	307	(79.7%)	385	(100%)
Total		220	(19.9%)	884	(80.1%)	1104	(100%)

2Q4 = 2 mg VTE every 4 weeks; 2Q8 = 2 mg VTE every 8 weeks

a % of patient population included for ethnicity comparison in the respective indication

b In the trial databases, patients with White race are categorized as "White"

Absolute treatment differences between Asians and Whites showed generally similar efficacy trends between treatment groups. This was confirmed by consistent overlaps of the corresponding 95%

confidence intervals for all comparisons (see Table 17). A tendency to numerically slightly more variable results of differences was seen the Asian subgroups.

Table 17 – Treatment Difference for VTE minus Control Overview for Week 52

Results at Week 52 relative to baseline

"Asian" restricted to subjects living in Asia or Australia; "White" restricted to subjects living in Europe,

			wet AMD VIEW 2	**CRVO** GALILEO	**DME** VIVID DME
		Control	Ranibizumab	Sham	Laser
			% difference (95% C.I.)		
Gain	**≥ 5 letters**	Asian	2.5 (-17.6; 22.5)	40.8 (10.8; 70.7)	51.0 (29.7; 72.3)
		White	-5.7 (-14.8; 3.5)	32.0 (14.8; 49.2)	33.3 (22.0; 44.7)
	≥ 10 letters	Asian	-3.6 (-24.8; 17.6)	46.4 (17.4; 75.4)	29.1 (8.1; 50.0)
		White	-7.9 (-17.7; 1.8)	23.7 (5.4; 42.0)	27.9 (16.9; 38.9)
	≥ 15 letters	Asian	-8.5 (-28.7; 11.7)	42.6 (13.2; 72.0)	16.5 (0.6; 32.5)
		White	-9.6 (-18.7; -0.5)	18.5 (-0.2; 37.2)	26.5 (18.1; 34.8)
Loss	**< 15 letters**	Asian	3.1 (-3.0; 9.2)	22.8 (-1.5; 47.2)	4.0 (-3.8; 11.8)
		White	-0.5 (-4.9; 4.0)	18.2 (6.7; 29.7)	11.3 (4.9; 17.6)
	≥ 0 letters	Asian	-7.4 (-24.2; 9.4)	-34.1 (-64.5; -3.7)	-42.3 (-63.3; -21.4)
		White	-0.8 (-9.2; 7.5)	-30.9 (-47.2; -14.6)	-29.9 (-40.4; -19.4)
	≥ 5 letters	Asian	-3.6 (-15.2; 8.1)	-37.9 (-67.7; -8.2)	-22.1 (-39.6; -4.6)
		White	1.1 (-5.6; 7.9)	-25.3 (-39.7; -10.8)	-21.1 (-29.8; -12.3)
	≥ 10 letters	Asian	-0.2 (-7.5; 7.1)	-36.2 (-62.9; -9.4)	-10.1 (-23.6; 3.4)
		White	4.0 (-1.1; 9.0)	-25.0 (-37.9; -12.1)	-14.7 (-22.2; -7.2)
	≥ 15 letters	Asian	-3.1 (-9.2; 3.0)	-22.8 (-47.2; 1.5)	-4.0 (-11.8; 3.8)
		White	0.5 (-4.0; 4.9)	-18.2 (-29.7; -6.7)	-11.3 (-17.6; -4.9)
			Point estimate and 95% CI for contrast (LS means) (ANCOVA)		
Mean	**change in BCVA**	Asian	-1.08 (-6.42; 4.26)	15.87 (5.48; 26.25)	8.95 (4.41; 13.49)
		White	-2.03 (-4.51; 0.46)	12.55 (6.36; 18.73)	9.14 (6.87; 11.41)
Mean	**change in CRT**	Asian	-25.80 (-50.33; -1.27)	-159.91 (-257.04; -62.78)	-177.90 (-232.33;-123.48)
		White	-2.04 (-13.48; 9.40)	-116.18 (-174.34; -58.02)	-137.56 (-164.76;-110.36)

LOCF: Last observation carried forward: Missing values were replaced by the last observed post baseline values before the missing value.

- Proportion of subjects gaining / losing ≥5, 10 or 15 and more letters in BCVA

The results are summarised in Figure 5 and Figure 6.

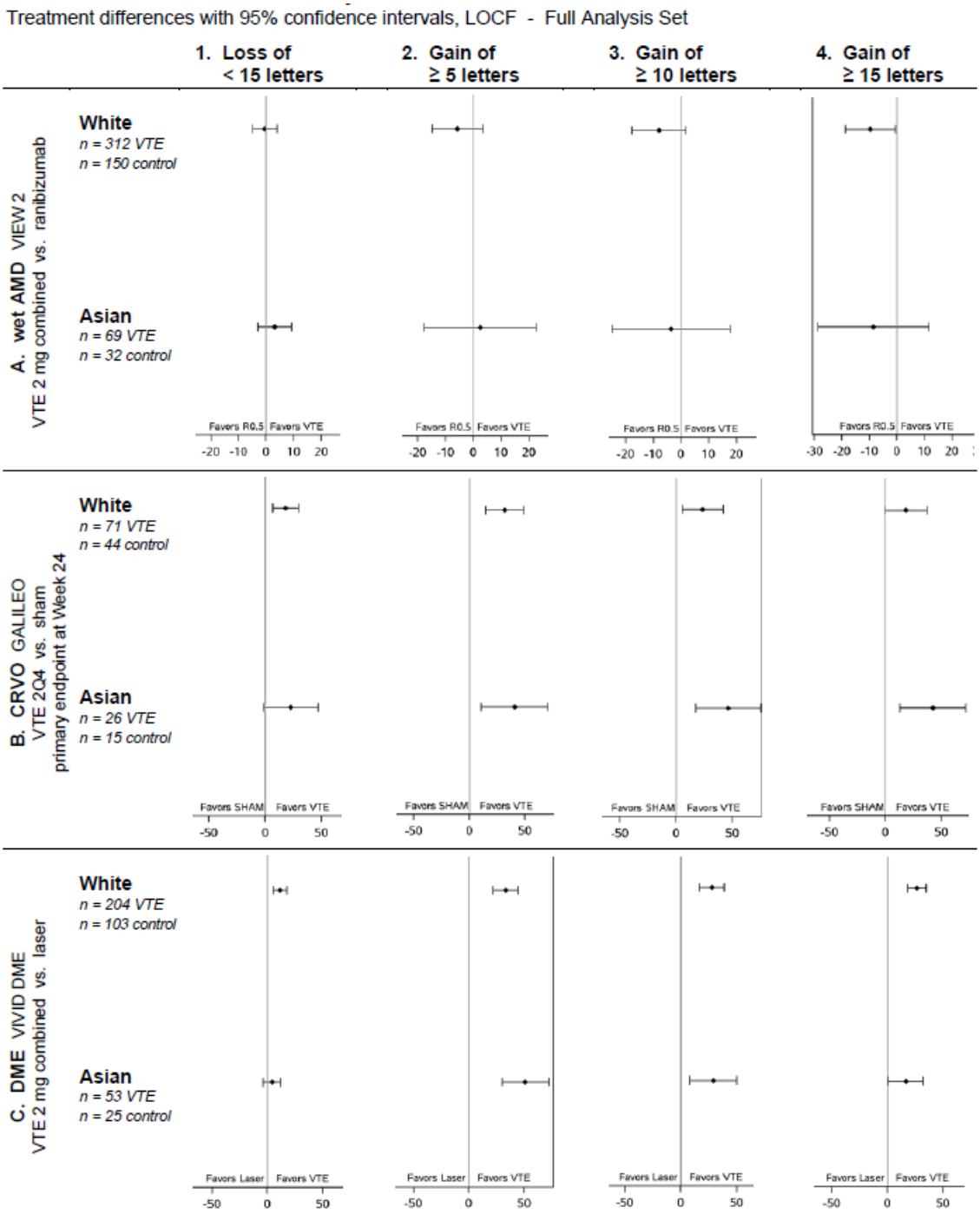


Figure 5 - Treatment Difference in Proportions of Subjects with BCVA categorical Gains/Losses from Baseline to Week 52 by race

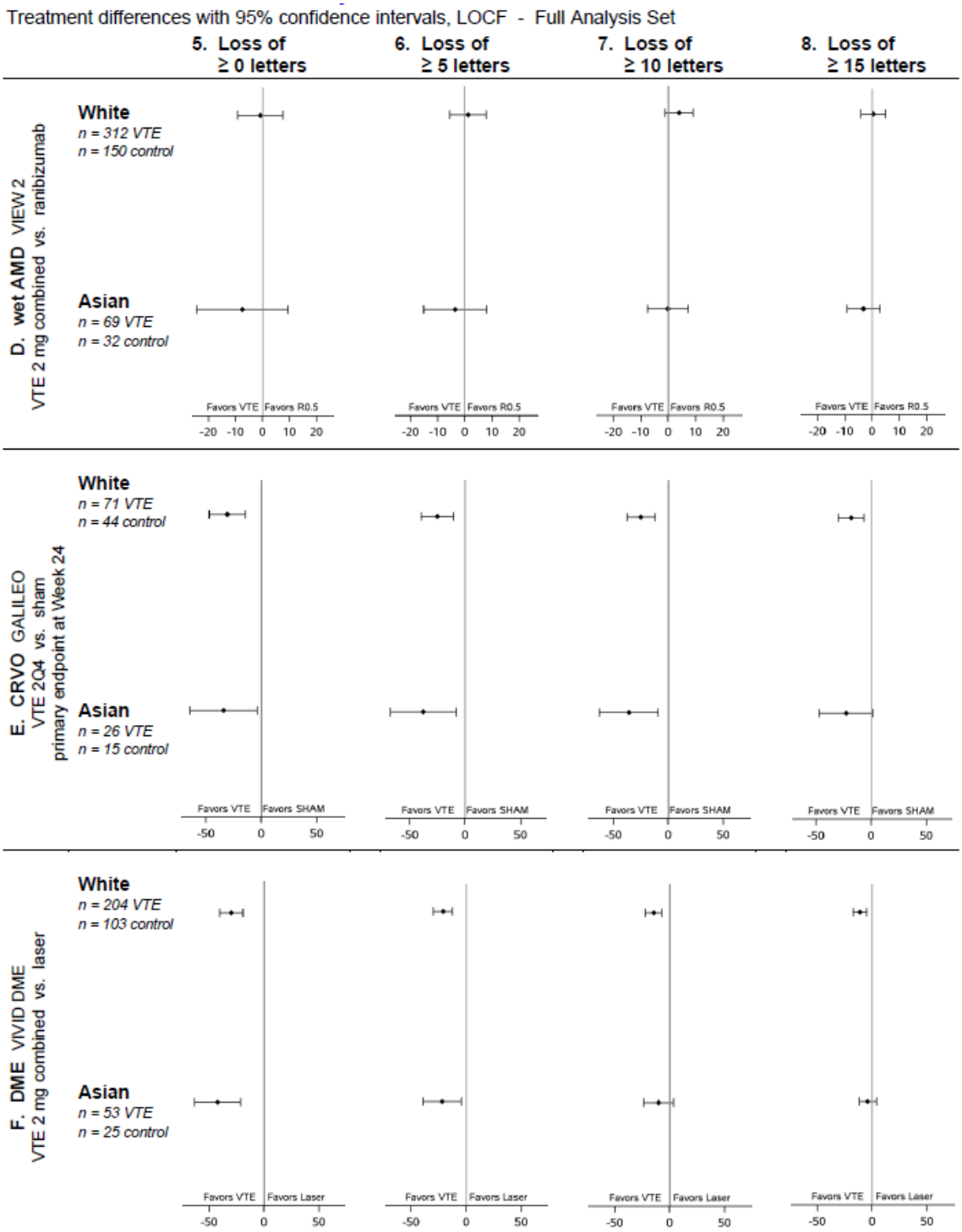


Figure 6 - Treatment Difference in Proportions of Subjects with BCVA categorical Gains/Losses from Baseline to Week 52 by race (continued)

- Change in BCVA from Baseline to Week 52

The results are summarised in Figure 7 and Table 18.

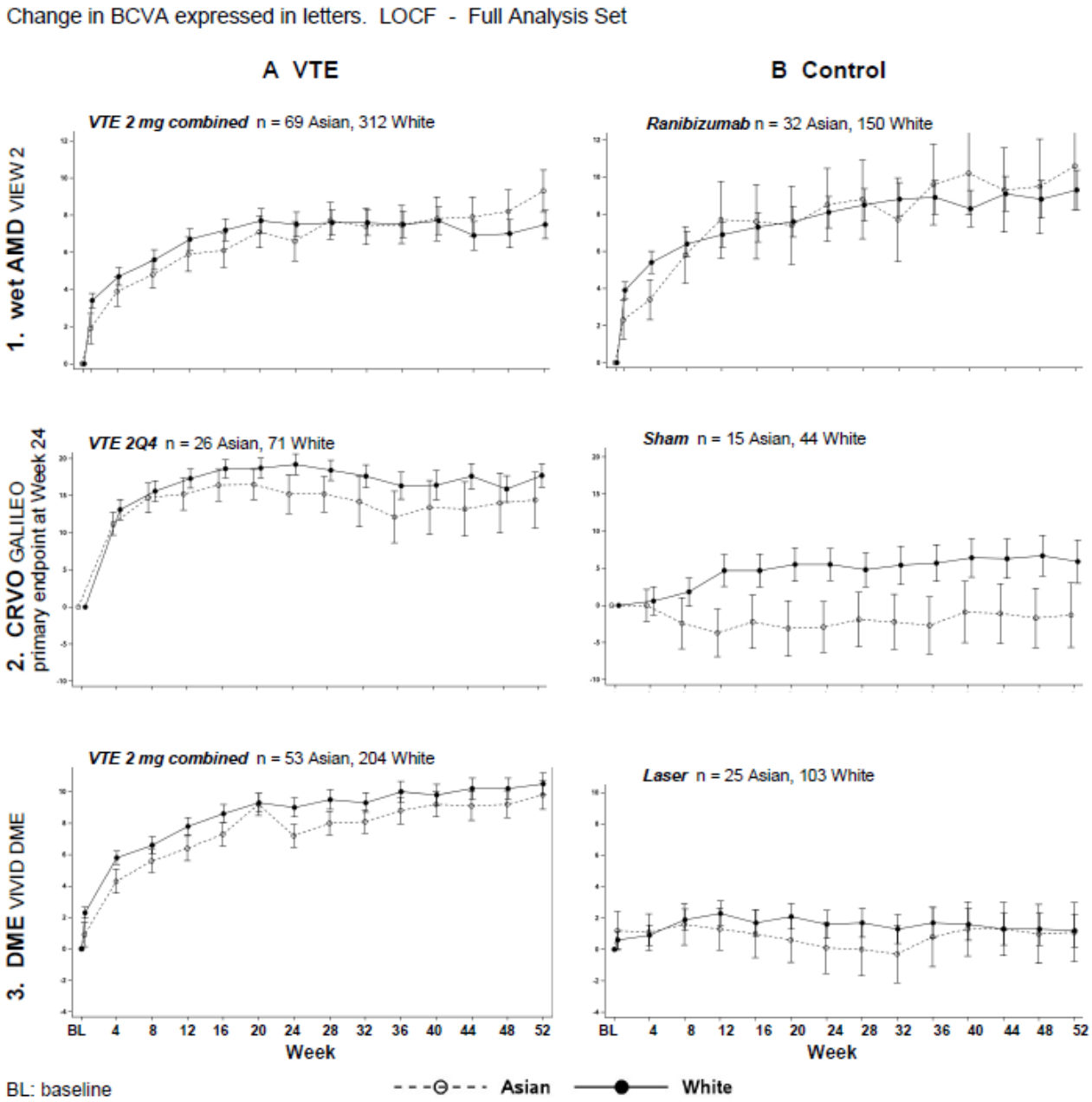


Figure 7 - Change in BCVA from Baseline to Week 52 by Race: Mean Values over Time

Table 18 - **Multiple Linear Regression for BCVA Change from Baseline to Week 52 (ETDRS letters)**

Analysis restricted to Asian subjects living in Asia and White ("White") subjects living in Europe. FAS. LOCF

Indication Study	Race	Treatment	n	Baseline means	LS Mean change	Contrast VTE versus Control (LS means) Point estimate (95% CI)	p-value [1]
Wet AMD VIEW 2	Asian	Ranibizumab	32	54.63	11.99	-1.38 (-6.73; 3.97)	0.6135
		VTE 2 mg combined	68	56.24	10.61		
	White	Ranibizumab	146	54.60	11.03	-1.96 (-4.48; 0.56)	0.1270
		VTE 2 mg combined	306	53.62	9.07		
CRVO GALILEO	Asian	Sham	15	53.20	-2.55	12.78 (2.36; 23.20)	0.0166
		VTE 2Q4	25	53.52	10.23		
	White	Sham	44	50.14	2.71	11.63 (5.48; 17.78)	0.0003
		VTE 2Q4	70	53.73	14.34		
DME VIVID DME	Asian	Laser	25	57.84	0.23	8.73 (4.27; 13.19)	0.0001
		VTE 2 mg combined	53	58.91	8.96		
	White	Laser	102	61.15	0.52	8.92 (6.68; 11.15)	<.0001
		VTE 2 mg combined	199	60.15	9.44		

[1] F-test, H0: No difference between treatment groups.

Note: Statistical model: Change from baseline to week 52 = Baseline + Treatment + Race + Age + Gender + Medical history of hypertension + Renal impairment + Treatment * Race.

P value for interaction of treatment and race in each indication is 0.8472 (wet AMD), 0.8501 (CRVO), and 0.9431 (DME).

- Change in central retinal thickness (CRT)

The results are summarised in Figure 8 and Table 19.

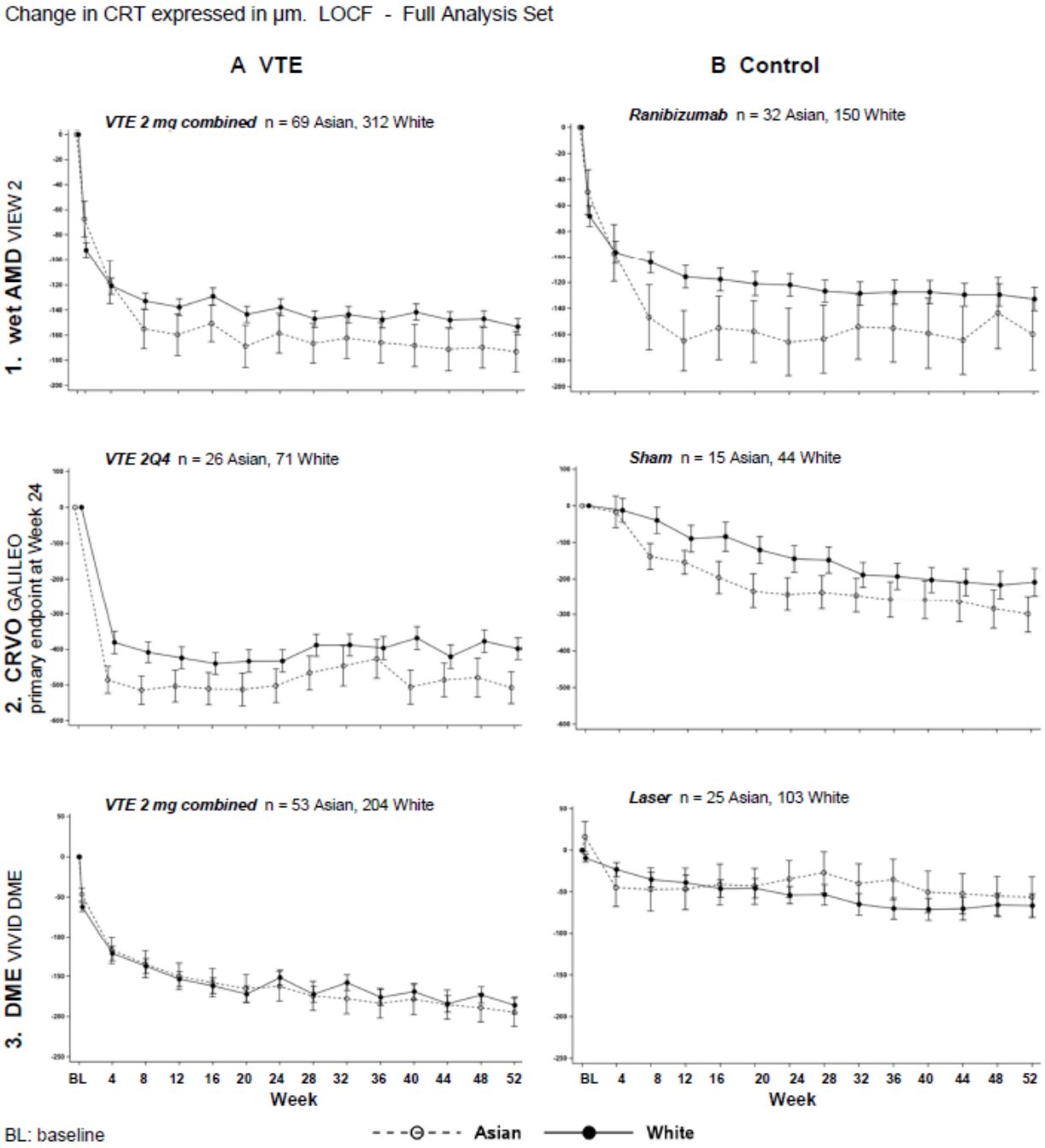


Figure 8 - Mean Change in CRT from Baseline to Week 52 by Race

Table 19 - Multiple Linear Regression for CRT Change from Baseline to Week 52 (ETDRS Letters)

Analysis restricted to Asian subjects living in Asia and White ("White") subjects living in Europe. LOCF

Indication Study	Race	Treatment	n	Baseline means	LS Mean change	Contrast VTE versus Control (LS means) Point estimate (95% CI)	p-value [1]
Wet AMD VIEW 2	Asian	Ranibizumab	32	348.47	-148.19	-24.29 (-48.98; 0.39)	0.0538
		VTE 2 mg combined	68	333.46	-172.48		
	White	Ranibizumab	146	320.88	-139.86	-1.57 (-13.22; 10.07)	0.7907
		VTE 2 mg combined	304	341.05	-141.44		
CRVO GALILEO	Asian	Sham	15	686.19	-288.50	-175.76 (-281.07; -70.45)	0.0012
		VTE 2Q4	25	729.14	-464.26		
	White	Sham	43	610.17	-264.30	-146.24 (-209.10; -83.39)	<.0001
		VTE 2Q4	70	670.21	-410.54		
DME VIVID DME	Asian	Laser	25	566.80	-35.67	-178.52 (-233.38;-123.66)	<.0001
		VTE 2 mg combined	53	499.49	-214.19		
	White	Laser	102	538.29	-69.39	-135.84 (-163.38;-108.30)	<.0001
		VTE 2 mg combined	198	507.93	-205.23		

[1] F-test, H0: No difference between treatment groups.
Note: Statistical model: Change from baseline to week 52 = Baseline + Treatment + Race + Age + Gender + Medical history of hypertension + Renal impairment + Treatment * Race.
P value for interaction of treatment and race in each indication is 0.1033 (wet AMD), 0.6304 (CRVO), and 0.1715 (DME).

Impact of intrinsic factors

The assessment of the impact of intrinsic factors was mainly based the systematic review of intrinsic factors originating from the Phase III trial data of VTE in Asians and Whites (see above), as well as published literature.

Extrinsic factors

Extrinsic factors are factors associated with environment and culture, which may differ between geographic region and which may impact efficacy and safety of a drug.

The analyses of extrinsic factors included the following:

- IVT administration of VTE in retinal diseases in East Asia as compared to Europe (North America and Australia)
- The medical practice of the diagnosis and treatment of mCNV in East Asia as compared to Europe, North America and Australia

These analyses did not identify any extrinsic factors that would indicate the potential for ethnical sensitivity of VTE in East Asia as compared to Europe (or other geographic regions with a mainly White population including North America and Australia).

PK results

Exploratory subgroup analyses did not reveal any relevant influence of age, sex, BMI, renal function, medical history of hepatic impairment, or geographic region (Europe/Japan, Japan/non-Japan) on the plasma concentrations of free or bound aflibercept.

See section 2.3.2. for results from MYRROR.

Safety results

See section 2.5. safety in other populations (other indications).

2.4.3. Discussion on clinical efficacy

The efficacy assessment of this application was based on the results of the pivotal, randomized, Sham-controlled phase III study MYRROR including 122 Asian adult subjects with visual impairment due to mCNV who were followed over a period of 48 weeks. In addition, the MAH presented the result of a systematic review to support ethnic insensitivity of VTE treatment based on existing clinical data for Eylea in wet AMD, CRVO and DME patients.

No dose-response study was conducted. However, the CHMP considered the choice of a 2 mg dose appropriate as this was the same dose shown effective in all existing indications.

Design and conduct of clinical studies

The design of the pivotal MYRROR study was considered generally acceptable by the CHMP, albeit the study size was limited. The 3:1 ratio of randomisation adds further limitation to the size of the comparator arm (Sham) and subgroup analyses.

The choice of Sham as comparator was accepted by the CHMP, since, as explained by the MAH, vPDT was not an approved treatment in Japan, where the majority of subjects were recruited into the study. However, since in Europe, ranibizumab has been approved for treatment of vision impairment secondary to mCNV in 2013, potential future studies would be expected to use it as active comparator.

The population studied in MYRROR included only Asian patients, the majority of which were Japanese. Therefore, based on the results of MYRROR alone, no conclusions for the European population could be drawn. Additional data supporting the extrapolation of MYRROR to other ethnicities and geographic regions are discussed below.

The inclusion-exclusion criteria were appropriate to select subjects with Baseline characteristics representative of a severe myopic population naïve to treatment, with subfoveal or juxtafoveal mCNV. Patients with extrafoveal lesions and those who had previously undergone treatment with vPDT were not included and the CHMP considered that this should be reflected in SmPC section 4.4.

The study protocol specified an initial mandatory injection in the active treatment arm followed by additional VTE injections as needed, based on pre-defined retreatment criteria to be applied by the treating specialist. This approach was considered acceptable given the experience with other VEGF inhibitors.

The choice of efficacy variables and endpoints at Week 24 and 48 were also considered suitable by the CHMP, whereby patients in the Sham group switched to active treatment as of Week 24.

Demographic and disease baseline characteristics were generally balanced between the two treatment groups. The majority of subjects were female (n=92; 76.0%) and PM is known to occur more frequently in women than in men. The majority of the patients recruited had a recent diagnosis of mCNV (i.e. disease duration of <2 months) which was in line with the recommended management of mCNV to avoid an irreversible degradation of vision over time. The CHMP furthermore noted the large range of age from 27 to 83 years.

Nevertheless, there was a marked difference in the incidence of cataract in the study eye history between active and control patients with a higher incidence in the VTE 2 mg group (24.2%) compared to the Sham+VTE 2 mg group (6.5%). However, the difference was considerably reduced when applying the standardized MedDRA query (57.1% in the VTE group versus 38.7% for Sham) rather than only the PT ‘cataract’. Furthermore, the occurrence of active cataracts (i.e. not resolved before study enrolment or data missing) was broadly similar in both treatment arms (38.5% in the VTE group versus 25.8% for Sham). Therefore, and since both VA and CRT were similar in both treatment arms, the CHMP concluded that there was no meaningful difference between the two treatment groups.

The CHMP also noted that the non-ocular medical and surgical history profile of patients was not balanced between the treatment groups with a higher proportion of patients in the VTE group with prior or concomitant medications for treatment of the cardiovascular or neurological systems. However, data from a post-hoc efficacy analysis showed a favorable outcome both in the entire study population and in individual subgroups. The subgroups with prior or concomitant medications for treatment of cardiovascular or neurological systems generally had slightly smaller numerical improvements in BCVA compared to the overall population. Therefore, any imbalances with regard to the history of patients did not pose a risk of overestimating efficacy.

Efficacy data and additional analyses

The primary efficacy analysis at Week 24 showed that the treatment with Eylea was associated with a statically and clinically relevant beneficial effect, superior to Sham treatment. The mean change in BCVA from Baseline was 12.1 letters in the VTE group and -2.0 letters in the Sham group, resulting in a difference of 14 letters between groups ($p<0.0001$). With VTE treatment, a rapid increase in BCVA was observed as early as Week 4 that still progressed through 24 weeks, but more modestly later on. Between Week 24 and 48, the level of improvement was maintained or slightly improved in the VTE group. Similarly, there was an improvement in BCVA by 7.9 letters in the Sham+VTE group at Week 48 compared to Week 24, when patients in the Sham group started to receive active treatment. Notably, this improvement was less pronounced than in the VTE group at Week 24 compared to Baseline, suggesting that patients benefit from early treatment, while if mCNV is left untreated irreversible damage may occur. This is in line with previous findings for anti-VEGF agents and current mCNV treatment recommendations.

The results of the primary analysis were supported by the findings for the secondary endpoint, a responder analysis defining a group of patients with a clinically meaningful gain of 15 or more letters. The difference in responder rates between treatment groups at Week 24 was 29.2% demonstrating a significant superiority of VTE over Sham with a p-value of 0.0001. Analyses at Week 48 still favoured the VTE group, but the difference was less pronounced (CMH adjusted difference of 21%, $p=0.0308$), which can be ascribed to the beneficial effect of VTE treatment as of Week 24 in the Sham+VTE group.

An effect of VTE treatment was also demonstrated for anatomical outcomes. VTE treatment resulted in a reduction of CRT by -85.7 µm at Week 24 compared to Baseline, while CRT remained unchanged in the Sham group (-7.8 µm). The between-group difference of 77.9 µm in CRT was statistically significant in favour of active treatment ($p<0.0001$). Similar to the improvement in BCVA over time, there was a rapid reduction CRT in the VTE arm beginning at Week 4 which thereafter stabilized through Week 24 and was maintained until the end of the study at Week 48. As for BCVA, with the initiation of active treatment at Week 24, patients in the Sham+VTE group experienced an improvement in CRT mainly perceptible between Week 24 and Week 32 (-56.7 µm from Baseline). However, the improvement was less pronounced than in the VTE arm during the first 6 months.

Additional exploratory variables (change in CNV lesion size and in area of leakage, as well as quality of life) also showed results generally supportive of a beneficial effect of VTE treatment consistent with the primary and secondary efficacy analyses. Only very few patients in the VTE group lost 5 or more letters by Week 24 and no patients worsened by 10 letters and beyond, while this was the case for a quarter of all patients in the Sham group.

Sensitivity analyses generally confirmed the results on the FAS, LOCF.

Notably, 14% of patients in the VTE group only required 1 injection in the 48-week study period, and nearly 60% required no more than 3 injections. The most common reasons for re-treatment were new or persistent CNV or bleeding, and investigator's discretion. Overall, the mean number of active injections needed in the VTE arm over the total period of study was low with < 4.5 injections (3 for the first 6 months and thereafter only 1.5). An increased number of injections over the 24 or 48 weeks did not

seem to result in higher improvements in VA, but quite the opposite with more limited gains in VA. These data showed that in some patients the disease may be controlled with a single injection. Therefore, the recommended dosing regimen of an initial injection followed by additional doses as needed, based on visual and/or anatomic outcomes, at intervals of no less than 4 weeks, was agreed by the CHMP. However, the CHMP noted that this regimen differed from the recommendation for the others indications as no initial repeated monthly dosing was required. Drug exposure and number of IVT injections would therefore be considerably less in mCNV patients compared to other target populations of Eylea. In order to better understand drug use in European clinical practice including frequency of injections in the mCNV population compared to the other approved indications, the MAH proposed to include mCNV patients in the planned observational post-authorisation safety study (PASS). Primary objectives will include the utilization of intravitreal aflibercept in real-world clinical practice including injection frequency by indication. It is planned to enroll 20,000 patients (i) with a macular disease for any indication approved in the EU, (ii) who are naïve to treatment with steroids and anti-VEGF drugs and (iii) for whom the decision was made to initiate IVT treatment with aflibercept. Patients will be followed over an individual observation period of 3 years. This proposal was acceptable to the CHMP, though it was noted that the study protocol was still being reviewed at the time of this report.

In order to extrapolate the data from MYRROR which included only Asian patients, to the European population, the MAH carried out a systematic review of ethnic insensitivity of VTE following the ICH E5 guidance. The methodology used by the MAH was considered appropriate with regards to the choice of criteria among Asian and Caucasian populations and the data from previous VTE studies in AMD, CRVO and DME patients. The level of efficacy was broadly comparable between Asian and Caucasian patients across the three indications. While there was some variability in the results possibly due to the fact that some of the sample sizes were rather small, there was no evidence of a systematic difference between Asian and Caucasian patients. There were also no major differences between the ethnic groups with regards to PK and safety outcomes (see section 2.5.1. for the discussion on safety). There was a certain degree of descriptive heterogeneity when comparing the responses to treatment within the same indication (punctual assessment) in the two selected populations, albeit not reaching statistical significance. The finding was discussed in detail and found to be likely attributable to random variation. Furthermore, when considering the course of the entire period of treatment, the data were rather favoring the VTE Caucasian groups in either indication which was reassuring. Overall, there was no reason to suspect that intrinsic or extrinsic factors such as diagnostic methodology, environmental or cultural factors will affect the efficacy of Eylea in either group. It was reasonable to assume that the same applies to the mCNV indication and therefore, the CHMP agreed that the results of the MYRROR study could be extrapolated to the EU population. Nevertheless, the CHMP was of the view that the absence of data in non-Asian patients should be reflected in the SmPC. The CHMP further noted that inclusion of mCNV patients in the drug utilization study, while not primarily designed for efficacy, should contribute to further document the effects of Eylea in Caucasians.

2.4.4. Conclusions on the clinical efficacy

The CHMP considered that the available data were sufficient to support the application for use of Eylea in the treatment of adult patients with visual impairment due to mCNV. The pivotal MYRROR study provided highly convincing clinical and statistical findings for both visual and morphologic outcomes in the Asian, treatment-naïve population. Extrapolation of the study data to the European population was considered acceptable based on a systematic review conducted by the MAH suggesting that VTE treatment is not sensitive to Asian versus non-Asian race.

In order to better understand the use of Eylea including frequency of injections in European clinical practice, the MAH proposed to include mCNV patients in the planned observational PASS.

2.5. Clinical safety

Introduction

This evaluation of safety of VTE for the treatment of mCNV was mainly based on the 48 weeks data from the pivotal phase III study MYRROR. In addition, post-marketing safety data for VEGF Trap-Eye were presented with a cut-off date of 31 January 2014.

Further supportive data were available from the clinical development program of existing indications of Eylea (AMD, RVO and DME). This includes a large clinical safety database of 2230 AMD subjects, 291 CRVO subjects, 578 DME subjects and 91 BRVO subjects who had received Eylea.

In MYRROR, adverse events (AEs) were classified as

- Drug related: if there was a reasonable possibility that the event was caused by the study drug. A possible example of a drug-related AE would be a hypersensitivity reaction.
- Injection related: if there was a reasonable possibility that the event occurred as a result of the IVT injection or sham procedure. A possible example of an injection-related AE would be eye pain at the site of the injection
- Procedure related: if there was a reasonable possibility that the event occurred as a result of participation in the study but was not associated with the injection (i.e., VTE/sham) procedure. A possible example of a procedure-related AE would be bruising at the site of a blood draw.

Patient exposure

The SAF of MYRROR included all patients who received any study treatment (VTE or Sham). A total of 122 Asian subjects were randomized including 91 in the VTE group and 31 in the Sham+VTE group. Subjects were evaluated at 4-week intervals for safety.

As expected because of the treatment schedule with a planned longer exposure period in the VTE 2 mg group starting at Baseline, mean and median duration of exposure, mean cumulative amount of administered VTE, and mean injection volume were higher in VTE group compared to the Sham+VTE group (see Table 20). In the Sham+VTE 2 mg group, subjects did not receive their first active injection until Week 24.

Table 20 – Extent of Exposure through Week 48 in MYRROR (SAF)

	VTE 2 mg (N=91)	Sham+VTE (N=31)	Total (N=122)
Duration of VTE exposure (weeks)			
Missing observations	0	0	0
Mean ± SD	44.3 ± 10.2	40.3 ± 15.5	43.3 ± 11.9
Median	48.0	48.0	48.0
Min. - Max.	4-50	4-49	4-50
Total amount of VTE (mg)			
Missing observations	0	0	0
Mean ± SD	8.4 ± 6.1	6.1 ± 4.5	7.8 ± 5.8
Median	6.0	6.0	6.0
Min. - Max.	2-24	0-12	0-24
Total injection volume (µL)			
Missing observations	0	0	0
Mean ± SD	208.8 ± 153.0	151.6 ± 112.2	194.3 ± 145.5
Median	150.0	150.0	150.0
Min. - Max.	50-600	0-300	0-600

Max=Maximum, Min=Minimum, SD=Standard deviation

During the first 24 weeks of treatment, the mean total exposure to VTE in the VTE 2 mg group was

5.8 mg (standard deviation, SD=3.3), over a mean duration of 163 days (SD=24.8) and none in the Sham group.

Exposure by number of active injections is summarised in section 2.4.2. (Table 7) for the FAS.

During the first 24 weeks of the MYRROR study, 22% (20/91) of subjects in the VTE group (SAF) received only 1 active injection (at Baseline), and 74% of VTE subjects received 3 or fewer active injections. Over the whole duration of the study, 59% (54/91) of VTE subjects received 1-3 active injections, while this number was 45% (14/31) for the Sham+VTE 2 mg group, where active treatment only started at Week 24. By the end of the study, 75 subjects (82.4%) in the VTE 2 mg group and 24 subjects (77.4%) in the Sham+VTE 2mg group had received the complete set of 12 injections (i.e., active or sham).

The majority of subjects in both treatment groups completed the treatment for the first 24 weeks of the study, including 83 (91.2%) subjects in the VTE 2 mg group and 25 (80.6%) in the Sham group (see section 2.4.2. and Table 2 for disposition of study subjects). A total of 14 (11.5%) subjects discontinued the study treatment prior to Week 24. The most frequently reported primary reasons for premature discontinuation of the study drug in the first 24 weeks were adverse events in 3 (3.3%) subjects of the VTE 2 mg group and 2 (6.5%) in the Sham group.

Demographic characteristics were generally well balanced between the two treatment groups and are summarised in section 2.4.2. (Table 3) for the FAS.

Adverse events

The majority of patients (69.7%, n=85) in both treatment groups experienced AEs: 71.4% (n=65) in the VTE 2 mg group and 64.5% (n=20) in the Sham+VTE group (see Table 21).

The proportion of subjects with any treatment-emergent AEs (TEAEs) up to Week 48 was 67.2%. The incidence of TEAEs was lower in the Sham+VTE group (58.1%) than in the VTE 2 mg group (70.3%). This difference between treatment groups was mainly due to non-ocular TEAEs, which were reported for 38.7% of the Sham+VTE group compared with 58.2% in the VTE 2 mg group. This difference between treatment groups already exists in the analysis conducted on the Week 24 data, with an incidence of non-ocular TEAEs of 44.0% in the VTE 2 mg group vs. 32.3% in the Sham+VTE group.

Injection related TEAEs were reported slightly more frequently in the VTE 2 mg group (same as at Week 24), with 20% versus 13 % in the Sham+VTE group. Procedure related TEAEs occurred exclusively in the VTE 2 mg group, with 13% (n=12) compared with none in the Sham+VTE group.

Table 21 - Overview of Subjects with AEs in MYRROR through Week 48 (SAF)

Number of subjects with any	VTE 2 mg N=91 n (%)	Sham+VTE N=31 n (%)	Total N=122 n (%)
AE	65 (71.4)	20 (64.5)	85 (69.7)
Pre-treatment AE	10 (11.0)	3 (9.7)	13 (10.7)
TEAE	64 (70.3)	18 (58.1)	82 (67.2)
Post-treatment AE	3 (3.3)	2 (6.5)	5 (4.1)
Ocular TEAE	34 (37.4)	12 (38.7)	46 (37.7)
Study eye	29 (31.9)	11 (35.5)	40 (32.8)
Fellow eye	19 (20.9)	5 (16.1)	24 (19.7)
Non-ocular TEAE	53 (58.2)	12 (38.7)	65 (53.3)
Treatment related TEAE	9 (9.9)	2 (6.5)	11 (9.0)
Treatment related ocular TEAE	6 (6.6)	1 (3.2)	7 (5.7)
Study eye	6 (6.6)	1 (3.2)	7 (5.7)
Fellow eye	0 (0.0)	0 (0.0)	0 (0.0)

Number of subjects with any	VTE 2 mg N=91 n (%)	Sham+VTE N=31 n (%)	Total N=122 n (%)
Treatment related non-ocular TEAE	3 (3.3)	1 (3.2)	4 (3.3)
Injection-related TEAE	18 (19.8)	4 (12.9)	22 (18.0)
Injection-related ocular TEAE	18 (19.8)	4 (12.9)	22 (18.0)
Study eye	18 (19.8)	4 (12.9)	22 (18.0)
Fellow eye	1 (1.1)	0 (0.0)	1 (0.8)
Injection-related non-ocular TEAE	0 (0.0)	0 (0.0)	0 (0.0)
Procedure-related TEAE	12 (13.2)	0 (0.0)	12 (9.8)
Procedure-related ocular TEAE	6 (6.6)	0 (0.0)	6 (4.9)
Study eye	6 (6.6)	0 (0.0)	6 (4.9)
Fellow eye	0 (0.0)	0 (0.0)	0 (0.0)
Procedure-related non-ocular TEAE	8 (8.8)	0 (0.0)	8 (6.6)
Maximum intensity for ocular TEAE			
MILD	30 (33.0)	12 (38.7)	42 (34.4)
MODERATE	3 (3.3)	0 (0.0)	3 (2.5)
SEVERE	1 (1.1)	0 (0.0)	1 (0.8)
Maximum intensity for non-ocular			
TEAE MILD	46 (50.5)	11 (35.5)	57 (46.7)
MODERATE	6 (6.6)	1 (3.2)	7 (5.7)
SEVERE	1 (1.1)	0 (0.0)	1 (0.8)
Any SAEs	7 (7.7)	1 (3.2)	8 (6.6)
Treatment related SAEs	1 (1.1)	0 (0.0)	1 (0.8)
Injection-related SAEs	1 (1.1)	0 (0.0)	1 (0.8)
Procedure-related SAEs	1 (1.1)	0 (0.0)	1 (0.8)
Treatment-emergent (TE) SAEs	7 (7.7)	0 (0.0)	7 (5.7)
Treatment related TE SAEs	1 (1.1)	0 (0.0)	1 (0.8)
Injection-related TE SAEs	1 (1.1)	0 (0.0)	1 (0.8)
Procedure-related TE SAEs	1 (1.1)	0 (0.0)	1 (0.8)
AEs leading to discontinuation from study drug	5 (5.5)	2 (6.5)	7 (5.7)
AEs leading to interruption from study	4 (4.4)	0 (0.0)	4 (3.3)
Death	0 (0.0)	0 (0.0)	0 (0.0)

Table 22 – Number of Subjects with TEAEs from Baseline through Week 48 by primary MedDRA System Organ Class (SOC) and Preferred Term (PT) (SAF)

Primary system organ class PT (MedDRA version 16.0)	**VTE 2 mg N=91 n (%)**	**Sham+VTE N=31 n (%)**	**Total N=122 n (%)**
Any TEAE	64 (70.3)	18 (58.1)	82 (67.2)
Blood and lymphatic system disorders	1 1.1)	0 (0.0)	1 (0.8)
Cardiac disorders	2 (2.2)	0 (0.0)	2 (1.6)
Ear and labyrinth disorders	1 (1.1)	0 (0.0)	1 (0.8)
Eye disorders	34 (37.4)	12 (38.7)	46 (37.7)
Conjunctival haemorrhage	*10 (11.0)*	*1 (3.2)*	*11 (9.0)*
Dry eye	*7 (7.7)*	*2 (6.5)*	*9 (7.4)*
Eye pain	*7 (7.7)*	*1 (3.2)*	*8 (6.6)*
Posterior capsule opacification	*0 (0.0)*	*3 (9.7)*	*3 (2.5)*
Punctate keratitis	*6 (6.6)*	*4 (12.9)*	*10 (8.2)*
Gastrointestinal disorders	14 (15.4)	2 (6.5)	16 (13.1)
Nausea	*7 (7.7)*	*0 (0.0)*	*7 (5.7)*
General disorders and administration site conditions	1 (1.1)	1 (3.2)	2 (1.6)
Hepatobiliary disorders	2 (2.2)	1 (3.2)	3 (2.5)

Primary system organ class PT (MedDRA version 16.0)	VTE 2 mg N=91 n (%)	Sham+VTE N=31 n (%)	Total N=122 n (%)
Immune system disorders	1 (1.1)	0 (0.0)	1 (0.8)
Infections and infestations	24 (26.4)	8 (25.8)	32 (26.2)
Herpes zoster	*0 (0.0)*	*2 (6.5)*	*2 (1.6)*
Nasopharyngitis	*17 (18.7)*	*3 (9.7)*	*20 (16.4)*
Injury, poisoning and procedural complications	6 (6.6)	1 (3.2)	7 (5.7)
Investigations	3 (3.3)	2 (6.5)	5 (4.1)
Metabolism and nutrition disorders	6 (6.6)	1 (3.2)	7 (5.7)
Musculoskeletal & connective tissue disorders	8 (8.8)	0 (0.0)	8 (6.6)
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	2 (2.2)	0 (0.0)	2 (1.6)
Nervous system disorders	15 (16.5)	1 (3.2)	16 (13.1)
Dizziness	*5 (5.5)*	*0 (0.0)*	*5 (4.1)*
Headache	*6 (6.6)*	*1 (3.2)*	*7 (5.7)*
Psychiatric disorders	1 (1.1)	1 (3.2)	2 (1.6)
Renal and urinary disorders	1 (1.1)	0 (0.0)	1 (0.8)
Reproductive system and breast disorders	1 (1.1)	0 (0.0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	2 (2.2)	2 (6.5)	4 (3.3)
Skin and subcutaneous tissue disorders	5 (5.5)	0 (0.0)	5 (4.1)
Vascular disorders	6 (6.6)	0 (0.0)	6 (4.9)

[a]: PT is only presented, if a TEAE occurred at an incidence of ≥5% in either treatment group.
AEs are sorted in alphabetical order by primary SOC and PT. A subject is counted only once within each PT of any primary SOC.

Ocular TEAEs

By Week 48, ocular TEAEs had been reported in 37% of VTE 2 mg subjects compared with 39% in the Sham+VTE group. In both treatment groups, the incidence of ocular TEAEs was higher in the study eye than the fellow eye. The overall incidence of ocular TEAE in the study eye was 33% compared with 20% in the fellow eye. An overview of ocular TAEs at Week 24 and 48 is provided in Table 23 and Table 24.

After initiation of active treatment in the Sham+VTE group at Week 24, the incidence of ocular TEAEs in the study eye at Week 48 was similar between groups or even slightly lower in the VTE 2 mg group (from Week 24 to Week 48: 32% VTE 2 mg group vs. 36% Sham+VTE group; from Baseline to Week 24: 23% VTE 2 mg group vs. 19% Sham group).

As judged by the investigator, ocular TEAEs in the study eye were considered to be related to study drug in 6.6% of the subjects in the VTE 2 mg group compared with 3.2% of the subjects in the Sham+VTE group. In both treatment groups, ocular TEAEs in the study eye were about twice as often considered related to the injection procedure than the study drug. Injection-related TEAEs at Week 48 were still reported slightly more frequently in the VTE 2 mg group with 19.8% (Week 24: 16.5%) vs. 12.9 % in the Sham+VTE group (the latter incidence remained unchanged compared to Week 24). Procedure-related ocular TEAEs occurred exclusively in the VTE 2 mg group through Week 48 with 6.6% (Week 24: 5.5%) compared with none in the Sham+VTE group.

All but one ocular TEAE were mild (34.4%) or moderate (2.5%) in severity. One (0.8%) severe ocular TEAE in the study eye (macular hole, VTE 2 mg group) was also categorized as a serious adverse events (SAE) due to the need for hospitalization. It was the only SAE assessed as related to study drug, to a protocol-required procedure, and to the injection procedure. This event occurred in the second study period.

Table 23 - Number of Subjects with Ocular TEAEs in the Study Eye by primary SOC and PT through Week 24 (SAF)

Primary system organ class Preferred term MedDRA version 15.1	VTE 2 mg N=91 (100%)	Sham N=31 (100%)	Total N=122 (100%)
Number (%) of subjects with at least one ocular TEAE in study eye	21 (23.1%)	6 (19.4%)	27 (22.1%)
Eye disorders	21 (23.1%)	6 (19.4%)	27 (22.1%)
Anterior chamber cell	1 (1.1%)	0	1 (0.8%)
Blepharitis	1 (1.1%)	0	1 (0.8%)
Conjunctival haemorrhage	7 (7.7%)	1 (3.2%)	8 (6.6%)
Conjunctivitis	1 (1.1%)	0	1 (0.8%)
Conjunctivitis allergic	1 (1.1%)	0	1 (0.8%)
Corneal deposits	1 (1.1%)	0	1 (0.8%)
Corneal erosion	2 (2.2%)	1 (3.2%)	3 (2.5%)
Dry eye	1 (1.1%)	1 (3.2%)	2 (1.6%)
Eye allergy	0	1 (3.2%)	1 (0.8%)
Eye pain	6 (6.6%)	1 (3.2%)	7 (5.7%)
Ocular hyperaemia	2 (2.2%)	1 (3.2%)	3 (2.5%)
Photophobia	1 (1.1%)	0	1 (0.8%)
Punctate keratitis	4 (4.4%)	3 (9.7%)	7 (5.7%)
Retinal detachment	0	1 (3.2%)	1 (0.8%)
Retinal haemorrhage	1 (1.1%)	0	1 (0.8%)
Retinal tear	1 (1.1%)	0	1 (0.8%)
Retinoschisis	1 (1.1%)	0	1 (0.8%)

AEs are sorted in alphabetical order by primary SOC and PT. A subject is counted only once within each PT of any primary SOC.

Table 24 - Number of Subjects with Ocular TEAEs in the Study Eye by primary SOC and PT through Week 48 (SAF)

Primary system organ class Preferred term MedDRA version 16.0	VTE 2 mg N=91	Sham+VTE N=31 n (%)	Total N=12 N (%)
Any ocular TEAE in the study eye	29 (31.9)	11 (35.5)	40 (32.8)
Eye disorders	29 (31.9)	11 (35.5)	40 (32.8)
Conjunctival haemorrhage	10 (11.0)	1 (3.2)	11 (9.0)
Punctate keratitis	6 (6.6)	4 (12.9)	10 (8.2)
Eye pain	7 (7.7)	1 (3.2)	8 (6.6)
Dry eye	2 (2.2)	2 (6.5)	4 (3.3)
Corneal erosion	2 (2.2)	1 (3.2)	3 (2.5)
Ocular hyperaemia	2 (2.2)	1 (3.2)	3 (2.5)
Posterior capsule opacification	0 (0.0)	2 (6.5)	2 (1.6)
Retinoschisis	2 (2.2)	0 (0.0)	2 (1.6)
Anterior chamber cell	1 (1.1)	0 (0.0)	1 (0.8)
Blepharitis	1 (1.1)	0 (0.0)	1 (0.8)
Cataract subcapsular	1 (1.1)	0 (0.0)	1 (0.8)
Chorioretinal atrophy	0 (0.0)	1 (3.2)	1 (0.8)
Conjunctivitis	1 (1.1)	0 (0.0)	1 (0.8)
Conjunctivitis allergic	1 (1.1)	0 (0.0)	1 (0.8)
Corneal deposits	1 (1.1)	0 (0.0)	1 (0.8)
Eye allergy	0 (0.0)	1 (3.2)	1 (0.8)
Keratitis	1 (1.1)	0 (0.0)	1 (0.8)
Macular degeneration	1 (1.1)	0 (0.0)	1 (0.8)
Macular hole	1 (1.1)	0 (0.0)	1 (0.8)
Ocular discomfort	1 (1.1)	0 (0.0)	1 (0.8)
Photophobia	1 (1.1)	0 (0.0)	1 (0.8)
Retinal degeneration	1 (1.1)	0 (0.0)	1 (0.8)
Retinal detachment	0 (0.0)	1 (3.2)	1 (0.8)
Retinal haemorrhage	1 (1.1)	0 (0.0)	1 (0.8)

Primary system organ class Preferred term MedDRA version 16.0	VTE 2 mg N=91	Sham+VTE N=31 n (%)	Total N=12 N (%)
Retinal tear	1 (1.1)	0 (0.0)	1 (0.8)
Vitreous floaters	1 (1.1)	0 (0.0)	1 (0.8)
Vitreous haemorrhage	1 (1.1)	0 (0.0)	1 (0.8)
Investigations	0 (0.0)	1 (3.2)	1 (0.8)
Intraocular pressure increased	0 (0.0)	1 (3.2)	1 (0.8)

Adverse events are sorted in by frequency in the total group.
A subject is counted only once within each preferred term of any primary SOC.

Non-ocular TEAEs

The incidence of non-ocular TEAEs at Week 24 was 44.0% in the VTE 2 mg group and 32.3% in the Sham+VTE group. From Week 24 to Week 48, the incidence was 33.0% in the VTE 2 mg group and 12.9% in the Sham+VTE group. The proportion of subjects experiencing at least one non-ocular TEAE by Week 48 was still higher in the VTE 2 mg group with 58.2% versus 38.7% in the Sham+VTE With regard to SOC, the highest incidences of non-ocular TEAEs were seen for 'infections and infestations' (26.4% in the VTE 2 mg group and 25.8% in the Sham+VTE group), followed by 'gastrointestinal disorders' (15.4% in the VTE 2 mg group and 6.5% in the Sham+VTE group) and 'nervous system disorders' (16.5% in the VTE 2 mg group and 3.2% in the Sham+VTE group). Most of the non-ocular TEAEs were reported as single events.

The most commonly reported non-ocular TEAEs occurring in ⩾5% of all subjects were nasopharyngitis (18.7% VTE 2 mg; 9.7% Sham+VTE group), headache (6.6% VTE 2 mg; 3.2% Sham+VTE group), and nausea (7.7% VTE 2 mg; 0.0% Sham+VTE group).

Four subjects overall experienced a non-ocular TEAE considered to be related to the study drug (3 subjects in the VTE 2 mg treatment group and one subject in the Sham group). No non-ocular TEAEs were considered to be related to the injection. Eight subjects, all in the VTE 2 mg group, experienced a procedure-related, non-ocular TEAE. One subject in the VTE 2 mg treatment group was reported to have had a severe non-ocular TEAE, a cerebral haemorrhage that occurred in the first study period and was also categorized as SAE because of the need for hospitalization.

Table 25 - Number of Subjects with Common Non-Ocular TEAEs occurring in ⩾2% of Subjects by PT through Week 24 (SAF)

MedDRA SOC MedDRA PT	VTE 2 mg N=91 n (%)	Sham N=31 n (%)	Total N=12 n (%)
Number (%) of subjects with at least one non-ocular TEAE	40 (44.0%)	10 (32.3%0	50 (41.0%)
Headache	6 (6.6%)	1 (3.2%)	7 (5.7%)
Hypertension	4 (4.4%)	0[a]	4 (3.3%)
Nasopharyngitis	9 (9.9%)	2 (6.5%)	11 (9.0%)
Nausea	5 (5.5%)	0	5 (4.1%)
Upper respiratory tract infection	3 (3.3%)	0	3 (2.5%)

[a] One patient in the Sham group was reported to have had 'blood pressure increased'

Table 26 - Number of Subjects with Common Non-Ocular TEAEs occurring in ⩾2% of Subjects by PT through Week 48 (SAF)

Preferred Term MedDRA version 16.0	VTE 2 mg N=91 n (%)	Sham N=31 n (%)	Total N=12 n (%)
Any non-ocular TEAE	53 (58.2)	12 (38.7)	65 (53.3)
Nasopharyngitis	17 (18.7)	3 (9.7)	20 (16.4)
Headache	6 (6.6)	1 (3.2)	7 (5.7)
Nausea	7 (7.7)	0 (0.0)	7 (5.7)
Dizziness	5 (5.5)	0 (0.0)	5 (4.1)
Hypertension	4 (4.4)	0 (0.0)[a]	4 (3.3)
Back pain	3 (3.3)	0 (0.0)	3 (2.5)
Diarrhoea	2 (2.2)	1 (3.2)	3 (2.5)
Upper respiratory tract infection	3 (3.3)	0 (0.0)	3 (2.5)

[a] One patient in the Sham+VTE group was reported to have had 'blood pressure increased'

Adverse drug reactions (ADR)

ADRs were reported for all adverse reactions with a reasonable possibility of causality to the injection procedure and/or study drug. Those ADRs that were observed in the MYRROR study are shown in the following table:

Table 27 - ADRs during the MYRROR Study

System Organ Class	Preferred Term	Frequency n = 116 (100%)
Eye disorders (study eye only)	Conjunctival haemorrhage	9.5%
	Punctate keratitis	7.8%
	Eye pain	6.9%
	Corneal erosion	1.7%
	Ocular hyperaemia	1.7%
	Cataract subcapsular	0.9%
	Retinal tear	0.9%
	Vitreous floaters	0.9%

Serious adverse event/deaths/other significant events

- **Serious adverse events (SAEs)**

In the VTE 2 mg group, 7 of the 91 patients (7.7%) experienced a treatment-emergent SAE, including 3 patients (3.3%) with ocular and 4 patients (4.4%) with non-ocular SAEs.

Three (3) events were reported during the first 24 weeks of the study, but not considered related to study treatment. These were idiopathic thrombocytopenic purpura, cerebral haemorrhage and depression.

The case of severe cerebral haemorrhage occurred in a subject in the VTE 2 mg treatment group 3 weeks after the third injection of Eylea during the first study period and was categorized as SAE because of the need for hospitalization. The patients was a 58-year old woman without relevant medical history, who at the same time developed hypertension of moderate intensity. Both events were not considered as related to study drug. The idiopathic thrombocytopenic purpura of moderate intensity occurred in a subject with history of Sjogren's syndrome and required prolonged hospitalization. The case of mild depression required prolonged hospitalization and recovered after 10 days.

Between Week 24 and Week 48 of the MYRROR study, SAEs were reported in additional 4 subjects,

including CNV secondary to pathologic myopia, macular hole (2 subjects), and Moraxella-positive pneumonia.

One of the ocular SAEs (macular hole) occurred in the study eye, the other 2 ocular SAEs (macular hole and CNV) occurred in the fellow eye. The severe macular hole in the study eye was also categorized as SAE due to the need for hospitalization. It occurred 1 month after the first injection and was the only SAE assessed by the investigator as related to study drug, to a protocol-required procedure, and to the injection procedure and required vitrectomy. Both subjects with the SAEs macular hole continued treatment, but the subject with CNV in the fellow eye was discontinued. However, the case of macular hole in the study eye led to study drug interruption. The subject was recovering thereafter. For all other ocular SAEs, the investigators did not suspect any causal relationship in connection with the subjects' study participation.

Bacterial pneumonia was considered to be of moderate intensity and led to the subject's hospitalization. The subject recovered within 4 weeks. The SAE was not considered to be related to study drug treatment, but the treatment was temporarily interrupted. There were no non-ocular drug-related SAEs reported in any subject in either treatment group through week 48.

In the Sham+VTE group, the only SAE reported was 'visual acuity reduced' in one patient, which occurred in the study eye and was considered unrelated to treatment or injection.

Deaths

No subjects died during the entire study period of 48 weeks.

Adverse events of interest

AEs of interest were reviewed in line with the safety concerns in the risk management plan (RMP).

- Endophthalmitis (important identified risk)

No endophthalmitis cases were reported in the MYRROR study through Week 48.

- Any intraocular inflammatory eye reactions regardless of suspected aetiology (important identified risk in the RMP)

One patient experienced an intraocular inflammation in MYRROR. This patient belonged to the VTE 2 mg group. The underlying event (PT: Anterior chamber cell) was non-serious, of mild severity and had resolved.

- Transient intraocular pressure (IOP) increase (important identified risk)

No AE of increased IOP in the study eye were reported in MYRROR. Mean pre-injection IOP was considered to be normal at Baseline in both treatment groups (15.3 $\pm$ 2.7 mmHg in the VTE 2 mg group and 15.8 $\pm$2.8 mmHg in the Sham+VTE group). There were no relevant mean changes from Baseline at Week 48 in either treatment group. None of the study subjects experienced an increase by $\geqslant$10 mmHg in pre-dose IOP compared to Baseline or had reported an absolute IOP value of $\geqslant$35 mmHg at any time. The number of subjects with an absolute pre-dose IOP measurement of >21 mmHg was small at each visit in either treatment group, and no clinically meaningful changes over time or imbalances between treatment groups were observed.

- Retinal pigment epithelium tears or rips (important identified risk)

No cases of retinal pigment epithelium tears were reported in MYRROR.

- Retinal tear / detachment (important identified risk)

TEAEs pertaining to the group retinal tear / detachment were reported in one patient in the Sham+VTE

group (PT: retinal detachment) and in one patient in the VTE 2 mg group (PT: retinal tear). Both events were mild and non-serious; retinal tear was reported as resolved.

- Cataract, especially of traumatic origin (important identified risk)

One patient experienced cataract in MYRROR. This patient was treated in the VTE 2 mg group. The underlying event (PT: Cataract subcapsular) was non-serious and had a mild severity, but was not resolved. No injection-related (i.e., traumatic) cataracts were reported in MYRROR through Week 48.

- Hypersensitivity and immunogenicity (important identified risk)

No hypersensitivity cases were reported in the MYRROR study.

Samples for the assessment of ADAs were collected prior to treatment on Day 1, at Week 24, and at Week 48. The results are described in section 2.3.3.

By Week 48, in both treatment groups combined, 5 subjects experienced ocular TEAEs referring to the medical entity "non-infectious inflammatory eye reactions due to immunogenicity" (PTs: conjunctivitis, conjunctivitis allergic, eye allergy, and keratitis). In 4 subjects the event occurred in the study eye. These were 1 case each of conjunctivitis, allergic conjunctivitis, and keratitis (all in the VTE 2 mg group), and 1 case of eye allergy in the Sham+VTE group.

- Arterial thromboembolic events (ATE, important potential risk)

There was one TEAE during the study classified as an ATE. The subject in the VTE 2 mg group developed a severe cerebral haemorrhage resulting in prolonged hospitalization (serious event). The subject was reported as recovering at the time of database lock. At the same time, this subject developed hypertension of moderate intensity that was reported on the same day (but not adjudicated as ATE). The study drug was withdrawn and the subject was reported as recovering at the time of database lock. Neither event was considered related to study drug.

- Venous thromboembolic events (important potential risk)

No venous thromboembolic events were reported in the MYRROR study.

- Hypertension (important potential risk)

Hypertension was reported in 4 subjects (4%) in the VTE 2 mg group compared with 1 subject (3.2%) in the Sham group by Week 48. None of the reported events remained unresolved. The reported hypertension events were of mild or moderate intensity and no events were regarded as severe.

Mean systolic and diastolic blood pressure values in the MYRROR study did not change to a clinically relevant extent from Baseline to Week 48 in either treatment group.

- Proteinuria (important potential risk)

One case of proteinuria occurred in the VTE 2 mg group. The event was regarded as mild, non-serious, and resolved.

- Non-ocular haemorrhage (important potential risk)

By study end, 2 subjects in the VTE 2 mg group had experienced a TEAE pertaining to the group of non-ocular haemorrhage. The Anti-Platelet Trialists' Collaboration ATE event cerebral haemorrhage was considered serious and severe, while contusion was reported to be non-serious and mild. The 2 events were recovering/resolving and recovered/resolved, respectively.

- Medication error and misuse (important potential risk)

No cases of medication error and misuse were reported.

- Off-label use (important potential risk)

There were no reports of off-label use.

- Embryo-fetotoxicity (important potential risk)

There were no reports of embryo-fetotoxicity.

- Retinal haemorrhage (important potential risk)

One case of retinal haemorrhage in the study eye was reported in MYRROR. This event occurred in the VTE 2 mg group, was considered non-serious and mild, and was resolved.

Immunogenicity

See above and section 2.3.3.

Laboratory findings

Several haematology, clinical chemistry, and urinalysis parameters were tested at Screening, Week 12, Week 24, Week 36, and Week 48. No safety concerns emerged from laboratory findings in the MYRROR study. Laboratory abnormalities and other general safety parameters were determined to be consistent with the patients' underlying disease and medical history. One patient prematurely discontinued the study due to impaired liver function 7 months after the last active injection. The event was non-serious and considered by the investigator as not related to the study drug.

Safety in special populations

Intrinsinc factors

Several subgroup analyses were conducted to evaluate the effects of the following demographic and disease variables on safety, including race (Japanese vs. non-Japanese), gender, age, visual impairment, duration of disease, renal and hepatic impairment as well as medical history (diabetes mellitus, cataracts, hypertension, cerebrovascular, myocardial infarction).

- Race/ethnicity

MYRROR (mCNV)

Overall, there was a higher total incidence of TEAEs reported for Japanese subjects (90) with 71.1% compared to non-Japanese subjects (32) with 56.3%. However, less Japanese than non- Japanese subjects experienced ocular TEAEs in the study eye (31.1% vs. 37.5%) and in the fellow eye (14.4% vs. 34.4%). However, the percentage of Japanese subjects with non-ocular TEAEs was markedly higher than in non-Japanese subjects (60.0% vs. 34.4%).

The incidences of drug-related TEAEs, procedure-related TEAEs and injection-related TEAEs were consistently lower in Japanese than in non-Japanese subjects.

Other indications

In order to support the claim of ethnical insensitivity of VTE and thus extrapolation of the results of MYRROR from the Asian population recruited to European mCNV patients, the MAH performed a systemic review of efficacy, safety and PK results from previous clinical trial sin existing indications (AMD, CRVO and DME).

With regard to the general safety of VTE in the existing indications in Asians compared with Non-Asians, it was noted that the Asian subgroups were consistently smaller (see section 2.4.2. and Table 16 for an overview of the sample sizes). Thus, the probability of detecting less frequent AEs in the Asian subgroups was a priori more limited if compared to the Caucasian subgroup.

For any TEAE, Asian and White subjects with AMD and DME showed largely similar frequencies. For CRVO, TEAE frequencies showed a trend to lower frequencies in the Asian as compared to the White subgroup (69.2% vs. 85.9%); however, the sample size especially in the Asian subgroup was small.

For any TEAE of severe intensity, frequencies were largely similar per indication in the White and Asian subgroups. For any SAEs, frequencies were lower in Asian than in White subjects for AMD and DME, but higher in Asian than in White subjects for CRVO.

For drug-related TEAEs, frequencies were lower in Asian than in White subjects for AMD and CRVO, but higher in Asian than in White subjects for DME. For injection-related TEAEs, frequencies were higher in Asian than in Caucasian subjects for AMD and DME, but lower in Asian than in White subjects for CRVO.

Discontinuations due to AEs were more frequently recorded for Asian than for White subjects for all three indications.

- Gender

With the exception of a higher incidence of ocular TEAEs in the fellow eye (all were unrelated to the study drug, injection or study procedures) in men (30) than in women (92) with 30.0% vs. 16.3%, respectively, the TEAE experience did not markedly differ between these subgroups.

- Age

Age subgroups were analysed as follows: <45 years (N=22), ⩾45 to <55 years (N=24), ⩾55 to <65 years (N=34), ⩾65 to <75 years (N=31) and ⩾75 years (N=11).

There was a numerical trend towards slightly higher incidences of TEAEs in subjects older than 65 years. With regard to drug-, procedure-, or injection-related TEAEs, this trend was slightly reverse.

All age subgroups had a comparable proportion of subjects with ocular TEAEs in the study eye. The proportions of subjects with ocular TEAEs in the fellow eye ranged from 9.7% in the age group ⩾65 to <75 years to 27.3% in both the youngest and the oldest age groups.

As for all TEAEs, there was a trend toward higher incidences of non-ocular TEAEs with age.

Extrinsinc factors

No extrinsic factors were analyzed in the MYRROR study.

Use in pregnancy and lactation

No information was available regarding the safety of VTE in breast-feeding women, or in pregnant women and their foetuses. No pregnancies were reported during the entire course of the MYRROR study.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed in the mCNV clinical development program. Patients investigated in MYRROR received treatment for a variety of diseases common to this study population including diabetes, hypertension, hypercholesterolemia, glaucoma, renal disease, pulmonary disease, cardiovascular disease, and peripheral artery disease.

Discontinuation due to adverse events

A total of 3 subjects (3%) discontinued study drug treatment due to TEAEs before Week 24. Of these, 2 subjects were in the VTE 2 mg group (idiopathic thrombocytopenic purpura and cerebral haemorrhage) and 1 subject in the Sham group (impetigo contagiosa). By Week 48, a total of 5 subjects (4%) including 4 in the VTE 2 mg group and 1 in the Sham+VTE group, had discontinued treatment because of TEAEs. Additional cases between Week 24 and Week 48 (both in the VTE 2 mg group) included one case each of mild CNV in the fellow eye, and of mild abnormal hepatic function.

Integrated analysis of clinical trials data

For the determination of ADRs and related frequency assessment, the MAH provided an integrated analysis using data from pivotal clinical trials with VTE as follows:

- AMD: VIEW 1 (100 weeks of treatment) and VIEW 2 (96 weeks of treatment)
- CRVO: COPERNICUS (100 weeks of treatment) and GALILEO (76 weeks of treatment)
- DME: VISTA DME and VIVID DME (52 weeks of treatment in each study)
- BRVO: VIBRANT (52 weeks of treatment)
- Myopic CNV: MYRROR (48 weeks of treatment).

In the pooled dataset, a total of 3073 patients had been exposed to VTE. The following table summarises relevant TEAEs and their incidence estimated from the integrated analysis.

Table 28 – Incidence of relevant TEAEs

Primary system organ class	Preferred Term (MedDRA 17.0)	Frequency N=3073 (100%)
Any		56.3%
Eye disorders	Any	53.5%
	Abnormal sensation in eye	0.6%
	Anterior chamber flare	0.4%
	Blindness	<0.1%
	Cataract	6.3%
	Cataract cortical	0.9%
	Cataract nuclear	1.7%
	Cataract subcapsular	1.5%
	Conjunctival haemorrhage	24.3%
	Conjunctival hyperaemia	1.2%
	Corneal epithelium defect	0.6%
	Corneal erosion	1.0%
	Corneal oedema	0.9%
	Detachment of retinal pigment epithelium	2.8%
	Eye pain	9.8%
	Eyelid irritation	0.1%
	Eyelid oedema	1.3%
	Foreign body sensation in eyes	3.2%
	Iridocyclitis	0.2%
	Iritis	0.1%
	Lacrimation increased	3.6%
	Lenticular opacities	0.7%
	Ocular hyperaemia	3.3%
	Punctate keratitis	2.4%
	Retinal degeneration	2.1%
	Retinal detachment	0.7%
	Retinal pigment epithelial tear	1.1%
	Retinal tear	0.4%
	Uveitis	<0.1%
	Vision blurred	2.9%
	Visual acuity reduced	10.3%
	Vitreous detachment	6.5%
	Vitreous floaters	6.4%
	Vitreous haemorrhage	1.2%
	Vitritis	<0.1%
General disorders and administration site conditions	Any	4.2%
	Injection site haemorrhage	1.3%
	Injection site irritation	0.4%
	Injection site pain	2.7%
Immune system disorders	Hypersensitivity	0.3%

Primary system organ class	Preferred Term (MedDRA 17.0)	Frequency N=3073 (100%)
Infections and infestations	Any	0.2%
	Endophthalmitis	0.2%
	Hypopyon	<0.1%
Injury, poisoning and procedural complications	Any	1.3%
	Cataract traumatic	<0.1%
	Corneal abrasion	1.2%
Investigations	Intraocular pressure increased	6.8%

Post marketing experience

Eylea has been commercially available in the United States since November 2011 and in the European Union since November 2012, and in a number of other countries from 2012 onwards.

Based upon sales information through 31 December 2013, the number of vials sold worldwide was estimated to be 1,709,923. Each vial sold was considered to represent a single drug administration.

A total of 1382 spontaneous ADRs have been reported starting on the date of product availability in countries where Eylea has been commercially available until 31 January 2014. Of these 1382 spontaneous case reports, 1166 were medically confirmed reports by health care professionals and 216 were not medically confirmed. Out of the 1166 medically confirmed case reports, a total of 816 cases were serious. A total of 2482 AEs were reported (one case report may include more than one AE).

The MedDRA SOC with the greatest number of both serious and non-serious ADRs was Eye Disorder system (1382 events, or approximately 55.7% of all AEs reported); followed by General Disorders and Administration Conditions (225 events, 9.1%), and Infections and Infestations (215 events, 8.7%).

When looking at serious AEs only, eye disorders accounted for 58.8% of reported serious AEs followed by Infections and Infestations (15.1%) and Nervous System disorders (7.7%).

At the time of the receipt of this application the PSUR covering the period from 1 June 2014 to 30 November 2014 was under assessment by the Pharmacovigilance Risk Assessment Committee (PRAC). At the time of this report, the assessment was concluded and the PRAC was of the view that the overall benefit-risk balance of Eylea in the approved indications (AMD, CRVO DME, BRVO) remained positive. Cumulative data up to 30 November 2014 for relevant events occurring in mCNV patients included 8 ADRs of macular hole from post-marketing sources and 5 from company sponsored clinical trials, and 9 serious post-marketing cases of cerebral haemorrhage, which represents the third most frequent reported PT among non-ocular haemorrhage cases.

2.5.1. Discussion on clinical safety

The clinical safety of Eylea in the treatment of visual impairment in adult mCNV patients was mainly supported by data collected over a period of 48 weeks in the pivotal phase III MYRROR study. Within MYRROR, for a comparative analysis of the safety data between groups, the 24 week period was of greater value as by this point in time, patients in the Sham+VTE group had not yet received their first active injection. Additional data supporting the safety of Eylea IVT treatment was available from the clinical development program in AMD, RVO and DME as well as from post-marketing experience.

The CHMP noted that the total number of mCNV patients studied in MYRROR was rather limited (n=122), especially for the control (Sham) arm (n=31). According to international guidelines (ICH E1), a minimum of 100 patients exposed for a minimum of one-year period is considered acceptable. The sample size was further reduced by about 20% of non-completers by the end of the study, precluding the identification of rare events. Furthermore, no safety data were generated in mCNV patients after the first year of

treatment with VTE (last Visit in MYRROR at Week 48). Thus, no definite conclusion could be drawn on the safety of VTE long-term treatment, and therefore the CHMP requested that mCNV patients should be included in the PASS program. The risk management plan (RMP) was updated accordingly.

The MYRROR study only generated data in the East-Asian populations. However, based on the available evidence at the time of this report, including the results of a systematic review of ethnic (in-)sensitivity of Eylea treatment in Asian versus non-Asian patients, there was no basis to assume that intrinsinc or extrinsinc factors would cause differences in safety between ethnic subgroups. Thus, the CHMP was of the view that the safety data from MYRROR could be extrapolated to European patients. Nevertheless, the fact that only Asian people were studied should be reflected in SmPC section 4.8.

The majority of patients in both treatment groups experienced AEs and TEAEs. The proportion of subjects with any TEAEs up to Week 48 was 67.2%. The incidence of TEAEs was lower in the Sham+VTE group (58.1%) than in the VTE 2 mg group (70.3%). This difference between treatment groups was mainly driven by non-ocular TEAEs. However, some baseline imbalances in terms of medical history findings to the disadvantage of the VTE 2 mg group, such as hypertension, and the relatively small size of the Sham+VTE 2 mg group have to be considered in the safety assessment and interpretation of AE frequencies.

Injection related TEAEs were reported slightly more frequently in the VTE 2 mg group than in the Sham+VTE group, and procedure related TEAEs occurred exclusively in the VTE 2 mg group. Similar observations were made at Week 24 and 48. Overall, the CHMP considered that a presentation of TEAEs by number of previous active injections and by time to onset from first and last injection would have allowed for a more accurate analysis of the possible impact of the injections on TEAEs occurrence. Such presentation should be included in the next PSUR.

Ocular TEAEs were reported in both treatment groups to a similar extent, and, as expected, the incidence was higher in the study eye than the fellow eye. In both treatment groups, ocular TEAEs in the study eye were about twice as often considered by the investigator related to the injection procedure than the study drug. Ocular TEAEs in the study eye were all mild or moderate in intensity, except one severe and serious case of macular hole, which was considered by the study investigator related to study drug, to the procedure as well as to the injection. The CHMP acknowledged that high myopia is a risk factor for macular hole, which could also have caused the event. However, a causal relationship to the use of Eylea could not be entirely excluded in this case due to the temporal relationship, whereby the event occurred one month after Eylea injection. Based on this single report of macular hole, however, no firm conclusions could be drawn. Therefore, the CHMP considered that this AE should be further analysed in the next PSUR based on a cumulative review of the available data to decide if section 4.8 of the SmPC, serious adverse reactions related to the injection procedure, should be updated.

Other reported ocular events in MYRROR were expected, particularly those considered ADRs (conjunctival haemorrhage, eye pain, punctate keratitis, corneal erosion, ocular hyperaemia, cataract subcapsular, retinal tear, vitreous floaters), based on the known safety profile of Eylea. Except for punctate keratitis (common in the SmPC versus very common in the MYRROR study), the ADR frequencies observed in the study were generally in accordance with the SmPC. Based on an integrated analyses of the available clinical data from all indications at the time of this report, the CHMP furthermore agreed that ADR frequencies in SmPC section 4.8 and package leaflet (PL) section 4 should be updated from common to uncommon for cataract cortical and corneal oedema and from uncommon to rare for blindness and uveitis.

With regard to non-ocular TEAEs, the highest incidences were seen for the MedDRA SOCs ‘infections and infestations’ (nasopharyngitis, upper respiratory tract infection), ‘gastrointestinal disorders’ (nausea) and ‘nervous system disorders’ (headache). These non-ocular TEAEs did not raise a safety concern. However, the serious case of cerebral haemorrhage, while not considered related to study drug, triggered a request

by the CHMP for close monitoring of this AE in next PSURs. The SmPC of Eylea already included a class warning regarding an increased risk of bleeding events possibly related to systemic VEGF inhibition.

The CHMP furthermore noted 2 cases of hypertension that occurred in in the VTE 2 mg group and were considered related to study drug by the investigator. As hypertension is an important potential risk in the RMP of Eylea, and may be caused by systemic VEGF inhibition, the CHMP considered that this event should continue to be closely monitored in the next PSURs.

Finally, as done for other indications, the MAH updated the safety information in SmPC section 4.8 with the incidence of arterial thromboembolic events in mCNV patients, which was agreed by the CHMP.

The results of the subgroup analyses appeared broadly consistent with the results in the entire study population, however, the sample sizes were mostly too small to allow robust conclusions. The numerical trend towards slightly higher incidences of TEAEs in subjects older than 65 years was not considered clinically meaningful.

Overall, the safety data from the MYRROR study did not give rise for new safety concerns with VTE in the treatment of mCNV compared to the existing indications. In terms of exposure, as previously discussed (see section 2.4.3.), mCNV patients would be expected to receive fewer injections of Eylea compared to other target populations.

2.5.2. Conclusions on clinical safety

Based on the available safety data at the time of this report, the CHMP considered that the safety profile of Eylea in mCNV subjects was generally consistent with the known safety profile in other, approved target populations. The product information (PI) was updated in line with the data from MYRORR as well as an integrated analysis of all available clinical safety data. In conclusion, the CHMP was of the view that the avilable data were sufficient to support the safety of Eylea in the treatment of adult patients with visual impairment due to mCNV.

Nevertheless, due to the lack of safety data for long-term treatment beyond 1 year, the CHMP considered that mCNV patients should be included in the ongoing PASS program.

In addition, the MAH should closely monitor reports of AEs of cerebral haemorrhage and hypertension and submit with the next PSUR a cumulative review of cases of macular hole in order to discuss addition of this AE in section 4.8 of the SmPC among serious adverse reactions related to the injection procedure. Furthermore, a presentation of AEs by number of previous active injections and by time to onset from first and last injections should be provided with the next PSUR.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next PSUR should be submitted in accordance with the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 22 is acceptable. The joint CHMP-PRAC endorsed Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes. The CHMP endorsed the Risk Management Plan version

22 with the following content:

Safety concerns

Important identified risks	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Retinal tear / detachment • Cataract (especially of traumatic origin) • Hypersensitivity and immunogenicity
Important potential risks	• Arterial thromboembolic events including non-MI ATEs and cardiovascular ischemic events • Venous thromboembolic events • Hypertension • Proteinuria • Non-ocular hemorrhage • Medication error and misuse • Off-label use • Embryo-fetotoxicity • Retinal hemorrhage
Missing information	• Use of Eylea® in patients with uncontrolled glaucoma • Concomitant use of different anti-VEGF therapies and other therapies for wet AMD, CRVO, BRVO, mCNV, and DME. Concomitant use includes bilateral treatment with anti-VEGFs. • Long term safety beyond 2 years • Posology utilized in marketed use

Pharmacovigilance plan

Study / activity type, title and category (1-3)*	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
A Study to Evaluate Physician and Patient Knowledge of Safety and Safe Use Information for Eylea in Europe: An Observational Post Authorization Safety Study (PASS) Category 3	To evaluate: - The level of physicians' knowledge and understanding of key safety information contained in the prescriber guide and the IVT injection procedure video. - The level of patients' knowledge and understanding of the key safety information booklet and audio CD.	Endophthalmitis - Transient intraocular pressure increase - RPE tears - Cataract - Embryofetotoxicity - Medication error and misuse - Off-label use	Planned.	Submission of final protocol: 31-03-2015 CSR planned to be available 30-06-2017

Study 18218 Assessment of the safety and drug utilization of intravitreal aflibercept (EYLEA) in real world clinical practice. A Post- Authorisation Safety Study (PASS) Category 3	The primary objectives are: - To monitor the incidence, frequency and severity of ocular and non-ocular adverse events in patients with macular diseases treated with intravitreal aflibercept in the real world clinical setting. - To monitor the drug utilization of intravitreal aflibercept – in terms of injection frequency and proportion of bilateral treatment **Secondary objectives are:** - To monitor the incidence, frequency and severity of adverse events occurring after concomitant use of other therapies for the macular disease - To determine how disease activity is monitored including type and frequency of ocular tests - To understand the reasons for treatment and retreatment decisions - To monitor the proportion of offlabel use in unapproved indications	Adverse events, serious or non-serious, related or not related, ocular or non-ocular will be assessed. This includes arterial thromboembolic events (including non-MI ATEs and cardiovascular ischemic events). - Bilateral use of Eylea - Concomitant use of different anti-VEGF therapies and other therapies for wet AMD, CRVO, BRVO, DME and myopic CNV. - Off-label use - Long term safety beyond 2 years.	Planned, final protocol to EMA in Q3 2015	Interim study report: Q2 2020 Final CSR: Q4 2023
Review safety outcomes of Study BAY 86-5321/16598: An open-label, randomized, active controlled, parallel group, Phase-3b study of the efficacy, safety,	Safety and tolerability. Primary study objective: - To compare the efficacy of 2 mg Eylea administered by two different intravitreal (IVT) treatment regimens to	As a condition for approval, the EMA has required a study to assess every-othermonth dosing versus an extended-dosing regimen with no maximum limit to the treatment interval.	Approved by EMA in OCT 2014, first patient in expected in Q3 2015	Submission of final CSR on: 31-12-2018

and tolerability of 2 mg Eylea administered by intravitreal injections using two different treatment regimens to subjects with neovascular agerelated macular degeneration (nAMD)	subjects with nAMD)			
Study no. BAY 86-5321/17613: A randomized phase 3b study comparing 3 dosing regimens of intravitreal VEGF Trap-Eye in patients with diabetic macular edema. Category 1	- To assess whether treatment according to label, i.e., extended treatment intervals based on visual and anatomic outcomes ("treat and extend") and PRN treatment after at least one year of Eylea treatment according to label is noninferior to the studied treatment regimen of a fixed dosing every two months (2Q8). - Safety and tolerability.	Evaluation of the possibility to extend treatment beyond 2Q8 without impact on efficacy.	Protocol submitted to EMA in October 2014	Interim report submission date after 2nd year completion (in 2018) Submission of final CSR: 11-2019

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Endophthalmitis (likely infectious origin)	Please refer to section 4.3 Contraindications: Where it is mentioned that active or suspected ocular or periocular infection and active severe intraocular inflammation are contraindicated. Please refer to Section 4.8 and section 4.4 of the SmPC . Please refer to section 4.2 Posology and method of administration where it is mentioned that patients should report any symptoms suggestive of endophthalmitis.	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.
Intraocular inflammation	Please refer to section 4.3 Contraindications where active or suspected ocular or periocular infection and active severe intraocular inflammation are contraindicated. Please refer to section 4.8 Undesirable effects and section 4.4 Special warnings and precautions for use: Please refer to section 4.2 Posology and method of administration:	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Transient intraocular pressure increase	Please refer to section 4.8 Undesirable effects, section 4.4 Special warnings and precautions for use and section 4.9 Overdose.	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.
Retinal pigment epithelium tears	Please refer to section 4.8 Undesirable effects: Labeled as ADR (frequency category: common). Please refer to section 4.4 Special warnings and precautions for use.	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.
Cataract (especially of traumatic origin)	Please refer to section 4.4. Special warnings and precautions for use and section 4.8 Undesirable effects.	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.
Medication error and misuse	Please refer to section 4.2 Posology and methods of administration where clear method of administration is explained. Please refer to section 4.9 Overdose.	Educational program in order to raise physicians' awareness on identified and potential risks.
Off-label use	Provision of SmPC, in which the correct and approved use of Eylea is detailed.	Educational program in order to raise patients' and physicians' awareness concerning the correct use of Eylea.
Embryo-fetotoxicity	Please refer to section 4.4: Special warnings and precautions for use and section 4.6: Fertility, pregnancy and lactation.	Educational program in order to raise patients' and physicians' awareness on potential risks and need for contraception.
Retinal tear / detachment	Please refer to section 4.4. Special warnings and precautions for use: Intravitreal injection-related reactions and section 4.8 Undesirable effects.	None.
Hypersensitivity and immunogenicity	Please refer to section 4.3 Contraindications and section 4.8 Undesirable effects:	None
Arterial thromboembolic events (ATEs) including non-MI ATEs and cardiovascular ischemic events	Please refer to section 4.8 Undesirable effects and section 4.4 Special warnings and precautions for use.	None
Hypertension	Please refer to section 4.4: Special warnings and precautions for use.	None
Non-ocular hemorrhage	Please refer to section 4.4 Special warnings and precautions for use. .	None
Use of Eylea in patients with uncontrolled glaucoma	Please refer to section 4.4: Special warnings and precautions for use.	None
Venous thromboembolic events	None	None
Proteinuria	None	None
Retinal hemorrhage	None	None
Concomitant use of	None	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
different anti-VEGF therapies and other therapies for wet AMD, CRVO, BRVO, mCNV, or DME		
Long-term safety beyond 2 years	None	None
Posology utilized in marketed use	None	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, the warning on populations with limited data has been updated to include non-Asian and non-treatment naïve mCNV patients as well as mCNV patients with extrafoveal lesions. The Package Leaflet has been updated accordingly.

The main changes to sections 4.1, 4.2 and 4.8 of the SmPC are shown below (new text is shown in bold, deleted text as strike-through):

SmPC section 4.1 Therapeutic indications

Eylea is indicated for adults for the treatment of

- neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1),
- visual impairment due to diabetic macular oedema (DME) (see section 5.1)~~.~~**,**
- **visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).**

SmPC section 4.2 Posology and method of administration

Posology

(...)

Myopic choroidal neovascularisation

The recommended dose for Eylea is a single intravitreal injection of 2 mg aflibercept equivalent to 50 microlitres.

Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease.

The schedule for monitoring should be determined by the treating physician.

The interval between two doses should not be shorter than one month.

(...)

SmPC section 4.4 Special warnings and precautions for use

Populations with limited data

(...)

In myopic CNV there is no experience with Eylea in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions.

The full PI including all changes is appended to this report.

In addition, changes related to sections 5.1 and 6.6 of the SmPC have been updated to further condense the description of the pharmacodynamic effects and to amend the instructions for use including improved pictograms. Annex II was amended to ensure distribution of an updated physician information pack after introduction of the new indication, Some minor editorial and typographical amendments were also introduced throughout the SmPC and PL.

Finally, it was noted by the CHMP that SmPC section 5.1 was rather extensive whereas the SmPC guideline recommends a concise summary of relevant evidence from studies supporting the indications. Therefore, the CHMP recommended that the MAH should submit a proposal to shorten SmPC section 5.1 at the time of the next submission affecting the Annexes. The pharmacodynamic effects could be summarised with all indications in a single table. For efficacy, it should be considered if both tables and figures are necessary. In any event, the text should be reviewed, which should not be redundant with the tables. Footnotes should be limited to the essential.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the Eylea PL version of the vial presentation adopted with a previous variation introducing BRVO as a new indication. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

CNV secondary to PM is one of the major causes of visual impairment in young adults worldwide. The visual prognosis of mCNV patients is generally poor without treatment. Recent findings with anti-VEGF agents have shown promising results in that IVT treatment not only helped prevent disease progression but also led to relevant vision recovery.

The benefits of Eylea in the treatment in mCNV were investigated in a single phase III trial (MYRROR) over a period of 12 months (6 month for the primary efficacy assessment) using Sham as comparator. In this study, an initial injection of 2 mg VTE followed by additional injections based on pre-defined re-treatment criteria up to 6 months (24 weeks) resulted in clinically relevant visual improvements with patients receiving active treatment being able to read on average 14 letters more on a standard vision

chart compared to the Sham group. Furthermore, while 35 out of the 90 patients (38.9%) in the VTE group responded to treatment with a vision gain of ≥ 15 letters, only 3 of the 31 patients (9.7%) in the Sham group were responders. VTE treatment also reduced CRT while it remained increased under Sham, with difference between treatment arms of 80 µm by Week 24. Overall, all visual and morphologic endpoints in the study showed a similar trend of superiority of VTE over Sham.

The study furthermore showed that beneficial effects occurred early after treatment initiation and reached a plateau during the first 6 months. Both visual and anatomic improvements were maintained over the course of the study until its end by Week 48.

The proposed dosing regimen of an initial dose of 2 mg VTE IVT followed by additional injections as needed, based on visual and/or anatomic outcomes, at intervals of no less than 4 weeks, was considered appropriate by the CHMP as it was in line with the regimen used in MYRROR. Indeed, the clinical data suggested that some patients may be controlled with a single injection. In the active treatment arm, 14% of subjects required only a single injection in the 48-week study period, and nearly 60% required between 1 and 3 injections.

Taken together, the data from MYRROR convincingly demonstrated a clinically relevant benefit within the study population, which was representative of a severe treatment-naïve myopic population with sub- or juxtafoveal mCNV. The study was conducted in Asia and the vast majority of patients were Japanese. The selection of the Asian population was justified by the MAH by a higher frequency of PM in Asians. Nevertheless, the prevalence of myopia appears to be increasing in Europe and the CHMP noted that other recent studies with VEGF inhibitors included both Asian and non–Asian patients. In order to be able to extrapolate the data from the Asian population to the EU population, the MAH carried out a comprehensive evaluation of the ethnic (in-)sensitivity of VTE in Asians and Caucasians based on the available clinical data for Eylea in AMD, CRVO and DME. Overall, the analyses performed found no major difference between Asians and non-Asians and therefore the CHMP agreed that the results of MYRROR could be considered representative for patients in Europe as well.

Uncertainty in the knowledge about the beneficial effects

The MYRROR study did neither include patients with extrafoveal lesions, nor those who had previously undergone treatment with Visudyne photo-dynamic therapy (vPDT) and thus had recurrent mCNV. These limitations were reflected in sections 4.4 of the SmPC, as was the fact that all patients were of Asian origin.

The majority of patients were recruited into the study less than 2 months after diagnosis. Such early intervention is in line with the recommended management of mCNV to avoid irreversible degradation of vision over time. This was also shown in MYRORR, where patients in the Sham+VTE group, who had a delayed in the start of active treatment, experienced less pronounced visual and anatomic improvements. Nevertheless, the data suggested a beneficial effect also with later onset of IVT VTE treatment.

The CHMP furthermore noted that drug exposure and number of IVT injections might be considerably less in mCNV patients compared to other target populations of Eylea. In contrast to AMD, RVO and DME, patients with mCNV may only require a single injection to control the disease. No initial fixed monthly dosing is required. In order to better understand drug use including frequency of injections in European clinical practice, mCNV patients will be included in the planned observational study, which will evaluate drug utilization of intravitreal aflibercept in real-world clinical practice including injection frequency by indication. This was considered adequate by the CHMP.

Finally, MYRROR recruited exclusively Asian patients and while, overall, the evaluation of the ethnical insensitivity found no major difference between Asians and non-Asians, the CHMP was of the view that the lack of data in non-Asian patients should be reflected in the SmPC. Inclusion of mCNV patients in the

planned drug utilization study, while not primarily designed for efficacy, should also contribute to further document the effects of Eylea in Caucasians.

Risks

Unfavourable effects

The data from the pivotal phase III study MYRROR suggested that the safety profile of Eylea in the treatment of mCNV patients was consistent with the safety profile previously reported in other target populations, i.e. AMD, DME, and RVO patients. The most common ocular ADRs reported were conjunctival haemorrhage, punctate keratitis and eye pain, which were already known adverse reactions listed in SmPC section 4.8 of Eylea. No cases of endophthalmitis have been reported in MYRROR. Also similar to previous studies with Eylea in AMD, DME and RVO, the most common non-ocular TEAEs were nasopharyngitis, nausea and headache.

PK/PD data likewise showed no marked differences in systemic exposure between patients groups, i.e. mCNV, AMD and CRVO. There was also no sign of immunogenicity.

Concerning arterial thromboembolic events, no case was reported in the VTE 2 mg group in MYRROR excepted for one case of cerebral haemorrhage, but this event was not considered by the investigator related to study drug. The incidence of arterial thromboembolic events was reflected in SmPC section 4.8, in line with what has been done in the other indications.

Based on an integrated analysis of the safety data across the clinical trials programs, the CHMP agreed to change the ADR frequency for cataract cortical and corneal oedema from common to uncommon and for blindness and uveitis from uncommon to rare. SmPC section 4.8 was updated accordingly.

While MYRROR only recruited patients from Asia, there was no evidence supporting a difference in the safety profiles in Asian and non-Asian subjects. Thus, the CHMP agreed that the safety data could be extrapolated to European patients. Nevertheless, the fact that only Asian people were studied was reflected in SmPC section 4.8.

Uncertainty in the knowledge about the unfavourable effects

The number of patients with safety data in the new target population was rather limited with 122 patients including 91 patients treated with Eylea. This limited sample size precluded detection of rare adverse events. Furthermore, no data were generated for long-term treatment beyond 1 year. Therefore, the CHMP considered that additional data should be generated post-authorisation and requested that mCNV patients should be included in the ongoing PASS program in the RMP.

While the vast majority of ocular adverse events in MYRROR was mild or moderate, there was one severe and serious case of macular hole with a temporal relationship to the administration of Eylea injection. With high myopia being a risk factor for macular hole, the CHMP was of the view that this single case report was not sufficient to draw any firm conclusions on causality. Therefore, a cumulative review should be provided with the next PSUR. Furthermore, a presentation of AEs by number of previous active injections and by time to onset from first and last injections should be provided with the next PSUR. The CMHP also requested close monitoring of AEs in the next PSUR based on one case of cerebral haemorrhage not considered related to study drug and 2 cases of hypertension considered related to study drug, as these events could be linked to potential risks of systemic VEGF inhibition.

Effects Table

Table 29 - Effects Table for Eylea, extension of indication to mCNV (data cut-off for pivotal trial: 15 Aug 2013)

Effect	Short Description	Unit	VTE	Sham	Uncertainties / Strength of evidence	References
Favourable Effects						
BCVA	LS mean change from Baseline at Week 24	ETDRS letters	13.2	-0.9	Superiority over Sham at Week 24 ($p \leq 0.0001$) for both endpoints; effect of VTE treatment maintained at Week 48. Effect size of 10 - 15 letters considered clinically relevant. No data available for extrafoveal and recurrent CNV. Study conducted in Asian patients, but extrapolation to non-Asian (i.e. EU) population acceptable as no major racial sensitivities detected.	MYRROR Study; report on ethnic sensitivity (ICH E5)
	Proportion of responders with BCVA improvement $\geqslant$ 15 letters at Week 24 compared to baseline	%	38.9	9.7		
CRT	LS mean change from Baseline at Week 24	µm	-85.7	-7.8	Superiority over Sham at Week 24 ($p < 0.0001$), effect of VTE treatment maintained at Week 48.	MYRROR Study

Abbreviations: BCVA = Best corrected visual acuity; CNV = Choroidal Neovascularization; CRT = Central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; LS = Least squares.

Effect	Short Description	Unit	VTE	Uncertainties / Strength of evidence	References
Unfavourable Effects*					
Endophthalmitis (likely infectious origin)	Incidence of PT	%	0.3% (AMD) 0.3% (CRVO) 0.0% (BRVO) 0.0% (DME) 0.0% (mCNV#)	No cases reported in MYRROR#.	MYRROR, RMP vers. 22
Intraocular inflammation	Incidence of PTs within grouped term(1)	%	2.6% (AMD) 1.6% (CRVO) 0.6% (BRVO) 2.3% (DME) 1.1% (mCNV#)	1 case of anterior chamber cell in MYRROR# VTE group.	MYRROR, RMP vers. 22
Transient IOP increase	Incidence of PTs within grouped term(2)	%	7.8% (AMD) 13.6% (CRVO) 3.2% (BRVO) 10.2% (DME) 0.0% (mCNV#)	1 case of IOP increased reported in MYRROR# Sham group (3.2%).	MYRROR, RMP vers. 22
Retinal pigment epithelial tears	Incidence of PT	%	1.9% (AMD) 0.0% (CRVO) 0.0% (BRVO)	No cases reported in MYRROR#.	MYRROR, RMP vers. 22

			0.0% (DME) 0.0% (mCNV#)		
Retinal tear/ detachment	Incidence of PTs -Retinal tear -Retinal detachment	%	1.2% (AMD) 1.3% (CRVO) 0.0% (BRVO) 0.7% (DME) 1.1% (mCNV#)	2 cases reported in MYRROR#: 1 case of retinal tear (VTE group, 1.1%); 1 case of retinal detachment (Sham, 3.2%).	MYRROR, RMP vers. 22
Cataract (especially traumatic)	Incidence of PT within grouped term(3)	%	all cataracts: 12.8% (AMD) 7.6% (CRVO) 4.4% (BRVO) 17.9% (DME) 1.1% (mCNV#) - traumatic cataracts: 0.8% (AMD) 0.04% (CRVO) 0.09% (BRVO) 2.2% (DME) 0.0% (mCNV#)	1 case of cataract subcapsular (but no injection-related/ traumatic cataracts) reported in MYRROR# VTE group.	MYRROR, RMP vers. 22

* The safety profile of Eylea in mCNV was broadly in line with the known safety profile at the time of this report (based on AMD, DME and RVO data). The list of unfavourable effects is based on the important identified risks in the RMP. Incidence rates are provided by indication (AMD, CRVO, BRVO and DME) based on RMP version 22, as adopted with this procedure.

The limited size of the safety database in mCNV patients precludes the detection of rare events and realistic frequency estimation.

(1) PTs included in grouped term 'Intraocular inflammation': Anterior chamber cell, anterior chamber flare, anterior chamber, inflammation, aqueous fibrin, chorioretinitis, choroiditis, cyclitis, eye inflammation, hypopyon, intermediate uveitis, iridocyclitis, iritis, non-infectious endophthalmitis, ocular vasculitis, pseudoendophthalmitis, retinal vasculitis, retinitis, uveitis, vitreal cells, and vitritis.

(2) PTs included in grouped term 'Transient IOP increased': IOP increased and Ocular hypertension. Incidence rates refer to these PTs irrespective of outcome (i.e. 'resolved' for evaluation of occurrence 'transient').

(3) PTs included in grouped term 'cataract': Atopic cataract, cataract, cataract cortical, cataract diabetic, cataract nuclear, cataract operation, cataract subcapsular, cataract traumatic, intraocular lens implant, lens capsulotomy, lens discolouration, lens extraction, lenticular opacities, lenticular operation, posterior lens capsulotomy, radiation cataract, and toxic cataract.

Abbreviations: AMD = Age-related macular degeneration; B/CRVO = Branch/central retinal vein occlusion; DME = Diabetic macular edema; IOP = Intraocular pressure; PT = Preferred Term (MedDRA vers. 17.0); TEAE = Treatment emergent adverse event

Benefit-Risk Balance

Importance of favourable and unfavourable effects

In the management of mCNV, both recovery of vision and prevention of further vision loss are important treatment objectives. Similar to what has been described for other anti-VEGF agents, IVT treatment with Eylea resulted in highly convincing findings for both visual and anatomic criteria supporting a clinically meaningful treatment benefit for mCNV patients, which may be achieved already with a single injection in some patients. Both the average gain in vision as well as the rate of responders clearly favoured Eylea over Sham and the findings were clinically relevant with treatment differences of 14 letters and 30% responders (BCVA gain ≥15 letters) between study arms.

Adverse events were mainly ocular and mild to moderate in intensity. No new safety concern arose. The safety profile of Eylea in mCNV patients appeared to be generally in line with the known safety profile in other target populations.

Benefit-risk balance

The benefits of Eylea in the treatment of mCNV have been convincingly demonstrated based on visual and anatomic finding showing that Eylea can prevent disease progression and help regain vision to a

clinically meaningful degree. The safety profile remained largely unchanged and the CHMP concluded that the benefits of Eylea in the treatment of adult patients with visual impairment due to mCNV outweighed its risks. Thus, the benefit-risk balance was considered to be favourable.

Discussion on the Benefit-Risk Balance

In light of the available reports for other VEGF inhibitors in mCNV, the efficacy findings for Eylea were not unexpected. At the time of this report, anti-VEGF agents had already become gold standard in the treatment of mCNV, with ranibizumab being the first in class approved in this indication in the EU in 2013.

Notably, the study population recruited in MYRROR was limited to Asians who were treatment-naïve and had subfoveal or juxtafoveal CNV. This was reflected in the SmPC. Furthermore, the safety database for mCNV patients was rather limited and no data for long-term treatment beyond 1 year were available. Therefore, the CHMP required that mCNV patients be included in the ongoing PASS program for Eylea as per the RMP. Furthermore, the inclusion of mCNV patients in the planned observational study will help to gain data on drug use in European clinical practice including frequency of injections in the new indication compared to the existing ones.

In addition, the CHMP considered that the MAH should closely monitor reports of AEs of cerebral haemorrhage and hypertension and submit the following safety data with the next PSUR:

- cumulative review of cases of macular hole in order to discuss addition of this AE in section 4.8 of the SmPC among serious adverse reactions related to the injection procedure.
- presentation of AEs by number of previous active injections and by time to onset from first and last injections.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include a new indication for adult for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV).
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated, including the warning on populations with limited data to inform healthcare professionals that no data were available for non-Asian and non-treatment naïve myopic CNV patients as well as patients with extrafoveal lesions. In addition, sections 5.1 and 6.6 of the SmPC have been updated to further condense the description of the pharmacodynamic effects and to clarify the instructions for use including improved pictograms. The Package Leaflet has been updated accordingly. Annex II was amended to indicate that an updated physician information pack should be distributed after introduction of the new indication. Minor editorial and typographical amendments were made throughout the product information.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the RMP.