Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for Aflibercept (rch)

## Proprietary Product Name: Eylea

## Sponsor: Bayer Australia Ltd

**August 2014**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

# About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# List of the most common abbreviations used in this AusPAR

| Abbreviation | Meaning |
|---|---|
| 2Q4 | 2 mg (of VTE) administered every 4 weeks |
| 2Q8 | 2 mg (of VTE) administered every 8 weeks |
| AE | Adverse event |
| AMD | Neovascular (wet) age-related macular degeneration |
| ATE | Arterial thromboembolic events |
| BCVA | Best corrected visual acuity |
| BRVO | Branch retinal vein occlusion |
| CFT | Central foveal thickness |
| CNV | Choroidal neovascularisation |
| CRT | Central retinal thickness |
| CRVO | Central retinal vein occlusion |
| ECG | Electrocardiogram |
| IOP | Intraocular pressure |
| IVT | Intravitreal |
| NV | Neovascularisation |
| NVD | Neovascularisation of the disc |
| NVE | Neovascularisation elsewhere |
| NVG | Neovascularisation glaucoma |
| NEI VFQ-25 | National Eye Institute 25-item Visual Function Questionnaire |
| OCT | Optical coherence tomography |
| PD | Pharmacodynamic |

| Abbreviation | Meaning |
|---|---|
| PK | Pharmacokinetics |
| PPS | Per protocol set |
| PRN | As needed |
| PRP | Panretinal photocoagulation |
| RVO | Retinal vein occlusion |
| SAE | Serious adverse event |
| SAF | Safety Analysis Set |
| TEAE | Treatment-emergent adverse event |
| TEAEI | Treatment-emergent adverse event of interest |
| VA | Visual acuity |
| VEGF | Vascular endothelial growth factor |
| VEGFR | VEGF receptor |
| VTE | VEGF Trap-Eye (Eylea) |

# I. Introduction to product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | Extension of indications and changes to the Product Information |
| *Decision*: | Approved |
| *Date of decision:* | 7 November 2013 |
| *Active ingredient:* | Aflibercept |
| *Product name:* | Eylea |
| *Sponsor's name and address:* | Bayer Australia Ltd<br>PO Box 903<br>Pymble NSW 2073 |
| *Dose form:* | Solution for intravitreal injection |
| *Strength:* | 40 mg/mL |
| *Containers:* | Vial with needle and Prefilled syringe |
| *Pack size:* | 1's |
| *Approved therapeutic use:* | *Eylea (aflibercept) is indicated in adults for the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).* |
| *Route(s) of administration:* | Intravitreal injection |
| *Dosage:* | Eylea treatment is initiated with one intravitreal injection per month. After the first three monthly injections, the treatment interval may be extended based on visual and anatomic outcomes. The interval between doses should not be shorter than one month. |
| *ARTG number:* | 180859 and 180860 |

## Product background

This AusPAR describes the application by Bayer Australia Pty Ltd to extend the indication of Eylea (aflibercept) to include the treatment of macular oedema following central retinal vein occlusion (CRVO). Aflibercept (VEGF Trap) is a recombinant fusion protein that binds and inactivates Vascular Endothelial Growth Factor (VEGF).

The current indication in Australia is:

> *Eylea (aflibercept) is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (wet AMD).*

In this application, the sponsor has proposed to add:

> *Visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).*

### Macular oedema following central retinal vein occlusion (CRVO)

After diabetic retinopathy, retinal vein occlusion (RVO) is the second leading cause of blindness due to retinal vascular disease. It affects about 5% of people older than 80 years. The two major categories are central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).

Visual loss due to CRVO is related to vascular permeability and leakage that develops after blockage of the retinal vein, leading to macular oedema, vitreous haemorrhage, neovascularisation and neovascular glaucoma. Fundus Fluorescein Angiography is used to assess severity of macular oedema and perfusion status. Optical coherence tomography is used to measure macular oedema and assess treatment response.

### Other treatments for macular oedema following central retinal vein occlusion (CRVO)

In Australia, Lucentis (ranibizumab) is the only non surgical treatment registered for the treatment of RVO (both CRVO and BRVO).

Laser photocoagulation has been used for more than 20 years for the treatment of BRVO, but is generally not recommended for the treatment of macular oedema associated with CRVO; although scatter laser photocoagulation has been recommended for the treatment of patients with anterior segment neovascularisation.

## Regulatory status

Eylea was approved in Australia for the indication of neovascular (wet) age-related macular degeneration in March 2012.

Similar applications have been approved in the USA and the European Union (see Table 1 below). A decision is pending in Switzerland.

**Table 1: International Regulatory Status of Eylea**

| Country | Submission Date | Approval date | Approved Indications & Approved Recommended Dosage for CRVO |
|---|---|---|---|
| **US**<br><br>NOTE: The US submission included the pivotal data from GALILEO and COPERNICUS at week 24. FDA-review of the week 24 to 76/100 data pending. | 2 May 2012 | 21 Sep 2012 | *Approved CRVO indication wording:*<br>EYLEA is indicated for the treatment of patients with …<br>1.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)<br>*Approved CRVO dosage:*<br>The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly) |
| **European Union**<br><br>MAA Centralised Procedure<br>Rapporteur: France<br>Co-Rapporteur: Germany<br><br>NOTE: The EU submission included the complete 76/100 week data from GALILEO and COPERNICUS. | 28 Nov 2012 | 26 Aug 2013 | *Approved CRVO indication wording:*<br>EYLEA is indicated for adults for the treatment of …<br>• visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)<br>*Approved CRVO dosage:*<br>The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres.<br>After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month.<br>If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended.<br>Monthly treatment continues until visual and anatomic outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered.<br>If necessary, treatment may be continued with gradually increasing treatment intervals to maintain a stable visual and anatomic outcome. If treatment has been discontinued, visual and anatomic outcomes should be monitored and treatment should be resumed if these deteriorate.<br>Usually, monitoring should be done at the injection visits. During treatment interval extension through to completion of therapy, the monitoring schedule should be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections. |
| **Switzerland** | 17 Dec 2012 | Pending | N/A |

### Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

# III. Nonclinical findings

## Introduction

The nonclinical part of the current submission comprised an embryofetal development study and a single-dose plasma kinetic study, conducted in rabbits by the subcutaneous (SC) route.

## Pharmacology

Aflibercept is a recombinant fusion protein constructed from binding domains of vascular endothelial growth factor A (VEGF) receptors 1 and 2 and the Fc region of a human Immunoglobulin G1 (IgG1). It acts as a soluble decoy receptor for VEGF A and placental growth factor 2 (PlGF-2).

No animal studies investigating the effect of aflibercept in CRVO were submitted. Therapy with Eylea for the proposed indication is rationalised by the demonstrated involvement of VEGF upregulation/release in the condition in response to retinal hypoxia, where it potently increases vascular permeability and contributes to exacerbation of the macular oedema.[1, 2] Intravitreal injection of VEGF has been shown to induce features of CRVO including vascular dilation, tortuosity, intra-retinal haemorrhage and capillary nonperfusion in the eyes of monkeys.[3]

## Pharmacokinetics

No new data was submitted.

## Toxicology

The change in dosing regimen proposed for the new indication does not impact the toxicological assessment made at the time of the original application to register Eylea, where animal: human exposure was compared over a month long human dosing interval. Intravitreal injection was found to be well tolerated in monkeys, with ocular inflammation seen that was generally mild, reversible, partly attributable to the vehicle itself and not considered to be toxicologically significant in the context of therapy. Other findings in the repeat-dose toxicity studies (including by the SC and intravenous (IV) routes, allowing very high animal: human exposure margins to be obtained) were largely attributed to the drug's pharmacological action (disrupting VEGF's role in microvascular maintenance) and were not considered to be of particular relevance to patients.

### Embryofetal development

The effect of aflibercept on embryofetal development was previously assessed in rabbits by the IV route. Treatment produced abortions, increased post implantation loss and

[1] Pe'er J., Folberg R., Itin A., Gnessin H., Hemo I. and Keshet E. (1998) Vascular endothelial growth factor upregulation in human central retinal vein occlusion. *Ophthalmology.* 105: 412–416.
[2] Pieramici D.J., Rabena M., Castellarin A.A., Nasir M., See R., Norton T., Sanchez A., Risard S. and Avery R.L. (2008) Ranibizumab for the treatment of macular edema associated with perfused central retinal vein occlusions. *Ophthalmology.* 115: e47–e54.
[3] Tolentino M.J., Miller J.W., Gragoudas E.S., Jakobiec F.A., Flynn E., Chatzistefanou K., Ferrara N. and Adamis A.P. (1996) Intravitreous injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate. *Ophthalmology.* 103: 1820–1828.

caused fetal malformations (external, visceral and skeletal), variations and impairment of ossification. No No Observable Effect Level (NOEL) for embryofetal development was established, with teratogenicity seen at all dose levels studied (≥3 mg/kg IV once every 3 days; relative exposure, approximately2900 with respect to peak plasma concentration ($C_{max}$) and approximately 680 with respect to area under the plasma concentration time curve (AUC) for free aflibercept in patients after intravitreal (IVT) administration of 2 mg to one eye). [Human reference values of 0.0193 µg/mL for $C_{max}$ and 2.856 µg·h/mL for $AUC_{0-28\,d}$, obtained in Clinical Study VGFT-OD-0702.

In the newly study, aflibercept was administered SC to rabbits on Days 1, 7 and 13 of gestation. Again, treatment-related malformations were observed at all dose levels investigated (≥0.1 mg/kg SC). Relative exposure at the Lowest Observed Effect Level (LOEL) was 13[4] with respect to plasma $C_{max}$ and 10[5] with respect to AUC. Fetal findings included cardiac ventricular septal defects (with or without malformation of major vessels), bifurcation or fusion of ribs, great parts of frontal, parietal and supraoccipital bones missing, multiple malformation of vertebrae, fusion of vertebral body, spina bifida, encephalomeningocele, and retarded ossification of digits/toes). The adverse effects on embryofetal development occurred in the absence of maternotoxicity.

### *Pregnancy classification*

The sponsor proposes no change to the existing pregnancy category (D). This is considered appropriate given the animal findings and considering the drug's anti-angiogenic activity. Category D is for drugs "*which have caused, are suspected to have caused or may be expected to cause, and increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details*".

### Nonclinical summary and conclusions

The nonclinical data comprised two new studies: a pilot pharmacokinetic study and an embryofetal development study, conducted by the SC route in rabbits.

The efficacy of aflibercept has not been investigated in an animal model of CRVO but is expected based on the recognised upregulation/release of VEGF in the disease.

Aflibercept was teratogenic in rabbits at all doses tested in the newly submitted SC study; these doses were not maternotoxic. Teratogenicity had been previously observed in rabbits in a study by the IV route submitted at the time of the drug's initial registration, which involved higher doses/ exposure levels. No NOEL for adverse effects on embryofetal development has been established. Relative exposure at the LOEL (0.1 mg/kg SC) is 10 (based on plasma AUC). Pregnancy Category D remains appropriate.

There are no nonclinical objections to registration of aflibercept for the indication of macular oedema following central retinal vein occlusion.

Amendments to the draft PI were recommended but these are beyond the scope of this AusPAR.

# IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

[4] Based on a peak level of 0.259 µg/mL measured in animals after dosing on GD13.
[5] Based on the sum of the $AUC_{0-t}$ values measured in animals after dosing on GD1 and GD13 (= 28.8 µg·h/mL).

## Introduction

### Clinical rationale

The rationale for aflibercept for the treatment of CRVO is based on the central role VEGF is considered to have in this disease. The increased retinal venous vascular pressure that results from CRVO causes transudation of plasma and blood, resulting in oedema and haemorrhages throughout all or most of the retina. Severe oedema appears to increase interstitial pressure and compromise arterial perfusion, resulting in variable amounts of capillary occlusion and cotton wool patches (nerve layer infarctions). The resulting retinal ischaemia leads to the production of inflammatory mediators such as VEGF, which increase vascular permeability and promote neovascularisation, leading to macular oedema. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF) with higher affinity than their natural receptors, inhibiting the binding and activation of these cognate VEGF receptors.

RVO is the second leading cause of blindness due to retinal vascular disease after diabetic retinopathy. There are two distinct types of RVO classified according to the site of occlusion, CRVO and BRVO and both conditions lead to permeability disorders of the retina caused by venous occlusion. It is estimated that RVO has a prevalence of 1% to 2% in persons older than 40 years of age and affects 16 million persons worldwide.[6] BRVO has been reported with a prevalence of about 3 times that of CRVO[7] and it has been estimated that CRVO affects approximately 2.5 million people worldwide.[8]

The prevalence (and incidence) of RVO is strongly associated with increasing age. Retinal vein occlusion is rarely seen in individuals younger than 50 years of age but may affect up to 5% of individuals over the age of 80 years. In an Australian population prevalence study, the age related increase in RVO prevalence was highly significant ($p<0.001$) and the prevalence for age specific cohorts was 0.7% for subjects < 60 years, 1.2% for subjects 60 to 69 years, 2.1% for subjects 70 to 79 years and 4.6% for subjects 80 years of age or older.7 In this study, the prevalence of RVO was 1.6% for both males and females and there was no significant sex difference after adjusting for age. In an Australian population aged 49 years and older, the 10 year incidence of RVO was 1.6% and significant predictors of incident RVO were age ≥ 70 years, increasing mean arterial blood pressure and atherosclerotic retinal vessels.[9] Risk factors for CRVO, reported by the Eye Disease Case-Control Study Group, include hypertension, diabetes mellitus, higher cardiovascular risk profile, and less physical activity.[10] Other possible risk factors predisposing to CRVO include age greater than 65 years[11], glaucoma or elevated intraocular pressure6,[11] renal disease6, dyslipidemia6, coagulopathy[11, 12] and smoking6. Inflammatory disease within the eye may also contribute to pathogenesis.[6]

The visual prognosis in macular oedema following CRVO is poor in a substantial proportion of patients, especially those with the ischaemic subtype. In patients with both

[6] Wong TY and Scott IU. Retinal-vein occlusion. *N Engl J Med*. 2010; 363:2135-44.
[7] Mitchell P, Smith W, and Chang A. Prevalence and associations of retinal vein occlusion in Australia: the Blue Mountains Eye Study. *Arch Ophthalmol*. 1996;114:1243-1247.
[8] Laouri M, Chen E, Looman M, Gallagher M. The burden of disease of retinal vein occlusion: review of the literature. *Eye.* 2011, 1–8.
[9] Cugati S et al. Ten-year incidence if retinal vein occlusion in an older population: the Blue Mountains Eye Study. *Arch Ophthalmol*. 2006;124:726-732.
[10] Aref AA, Scott IU. Management of macular edema secondary to central retinal vein occlusion: an evidence-based update. *Adv Ther*. 2011; 28(1):40-50.
[11] Channa R, Smith M, Campochiaro PA. Treatment of macular edema due to retinal vein occlusions. *Clinical Ophthalmology*. 2011;5:705–713.
[12] London NJS, Brown G. Update and review of central retinal vein occlusion. *Curr Opin Ophthalmol*. 2011; 22:159–165.

ischaemic and non ischaemic, CRVO baseline Visual acuity (VA) is generally poor (20/40) and in most patients it decreases over time.[13] The degree of retinal ischaemia is one of the major determinants of outcome in CRVO.[12] The principal causes of visual morbidity and complications of CRVO are macular oedema, vitreous haemorrhage, neovascularisation and neovascular glaucoma.[13] Macular oedema, with or without macular non-perfusion, is the most frequent cause of vision loss in patients with RVO[6] and is present to some degree in nearly all cases of CRVO.[12] There is a correlation between the severity of ischaemia and the risk of developing neovascularisation.[14] and CRVO can be complicated by neovascularisation of the iris or angle which may in turn lead to the development of neovascular glaucoma.

The most common presenting symptom of RVO is an abrupt, painless decrease in central visual acuity (VA) which varies in severity. Less commonly, patients may present with a history of transient vision loss, lasting a few seconds to minutes, with complete recovery of vision. These symptoms may recur over several days to weeks and are followed by a decrease in vision that can last for more than one year in some patients. The degree of vision loss depends on the extent of retinal involvement and on macular perfusion status. CRVO involves the entire retina, with scattered superficial and deep retinal haemorrhages, and venous dilation. In contrast, BRVO involves a more localised area of retina and is characterised by scattered superficial and deep retinal haemorrhages, venous dilation, intraretinal microvascular abnormalities and occluded and sheathed retinal venules.

In Australia, Lucentis (ranibizumab) is the only non-surgical treatment approved for the treatment of RVO (both CRVO and BRVO). Laser photocoagulation has been used for more than 20 years for the treatment of BRVO[12] and can provide vision stabilisation over the long-term and may enable some patients to read an additional 2 lines at 3 years compared with no treatment.[6] However, laser photocoagulation is generally not recommended for the treatment of macular oedema associated with CRVO, although scatter laser photocoagulation has been recommended for the treatment of patients with anterior segment neovascularisation.[1]

### Scope of the clinical dossier

The submission contained the following clinical information:

- 2 pivotal efficacy/safety studies:
  - GALILEO Weeks 24, 52 and 76 clinical study reports;
  - COPERNICUS Weeks 24, 52 and 100 clinical study reports.
- Integrated Analysis-Statistical Analysis Plans (6 months and 1 year data); Supportive Integrated Analysis for Posology (1 year data); Justification Document for Adverse Drug Reactions; Detailed Definition of Adverse Events of Interest (AEIs) and Selected Sub groups; Integrated Analysis (6 months and 1 year data); Supportive Integrated Analysis for Labelling; GALILEO adverse event (AE) Tables and Figures; COPERNICUS 0819 Tables and Figures.
- References.

[13] McIntosh RL, Rogers SL, Lim L, et al. Natural history of central retinal vein occlusion: an evidence-based systemic review. *Ophthalmology*. 2010; 117:1113-23.

[14] Campochiaro PA, Hafiz G, Shah SM, Nguyen QD, Ying H, Do DV, et al. Ranibizumab for Macular Edema Due to Retinal Vein Occlusions: Implication of VEGF as a Critical Stimulator. *Mol Ther*. 2008;16(4):791-9.

### Paediatric data

There is no paediatric development program for Eylea for the treatment of macular oedema following CRVO. The sponsor obtained a waiver from the European Paediatric Committee on the grounds that the CRVO only occurs in adults (EMEA-000236-PIP03-11). The absence of paediatric data is considered to be acceptable.

### Good clinical practice

The two pivotal efficacy and safety studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP).

## Pharmacokinetics

### Studies providing pharmacokinetic data

PK data were submitted for subjects with CRVO from the Phase III study GALILEO. In addition, the sponsor's Summary of Clinical Pharmacology included a post hoc comparison of PK data in subjects with CRVO and subjects with Neovascular (wet) age-related macular degeneration (wet AMD).

### Evaluator's overall conclusions on pharmacokinetics

After single and multiple (every 4 weeks) VEGF Trap-Eye (Eylea) ( VTE) 2 mg IVT injections administered to subjects with CRVO, systemic exposure to free and adjusted bound VTE was low. The low systemic exposures to VTE are unlikely to result in significant non ocular clinical effects. Furthermore, the PKs of VTE in subjects with CRVO and wet AMD are similar. Therefore, it is considered reasonable to extrapolate the known PK data for VTE in subjects with wet AMD to subjects with CRVO.

In the mandatory pharmacokinetic (PK) assessment (GALILEO), repeat administration of VTE resulted in free VTE trough plasma concentrations that were below the LLOQ in all subjects. The sponsor states that this result was expected because VTE is absorbed slowly from the eye into the systemic circulation where it binds to endogenous VEGF. Repeated administration of VTE 2 mg every 4 weeks through to Week 24 and then as required (PRN) up to Week 52 did not result in accumulation of the drug in plasma. Therefore, the PK results suggest no increased risk of systemic side effects with VTE following long term treatment. Exploratory sub group analyses with respect to age, sex, body mass index (BMI), creatinine clearance, hepatic impairment and geographical region could not be conducted because all free VTE plasma trough concentrations were below the lowest level of quantification (LLOQ).

In the mandatory PK assessment (GALILEO), following repeat VTE 2 mg IVT dosing at 4 week intervals adjusted VTE bound trough plasma concentrations increased from baseline (pre-dose) to Week 24 after which concentrations decreased through to Week 52. Exploratory sub group analyses of adjusted VTE bound aflibercept trough plasma concentration showed: higher concentrations in the 65 to < 75 years age group compared with the < 65 years age group at all time points; higher concentrations in females compared with males at all time points; and higher concentrations at Week 12 and 24 in subjects with mild renal impairment compared with subjects with normal renal function, with differences between the two groups at Weeks 36 and 52 being relatively small. None of the other sub group analyses resulted in noteworthy differences between subjects and subject numbers in some sub groups were too small for meaningful comparisons to be

made (for example, hepatic impairment, moderate and severe renal impairment, and subjects aged ≥ 75 years).

## Pharmacodynamics

Data relating to pharmacodynamic parameters of immunogenicity and changes in central retinal thickness (CRT) following treatment with VTE are discussed later in this CER (see also Attachment 2). These two parameters are considered to be directly relevant to the clinical efficacy and safety of VTE.

## Dosage selection for the pivotal studies

There was no dose ranging studies with VTE in subjects with CRVO submitted. The rationale for the final dose selection of VTE 2 mg via IVT injection every 4 weeks was based on the favourable safety and efficacy profile achieved using the same dosing regimen in the Phase II AMD study VGFT-OD-0508 (CLEAR-IT) and on the known disease characteristics of CRVO. The sponsor stated that, as the acute critical phase of CRVO is characterised by a larger area of leakage associated with higher intraocular VEGF levels than AMD, it was reasonable to expect that meaningful treatment results could be achieved within 6 months of treatment using the 2 mg dose at a 4 week interval. The sponsor also stated that VTE via IVT injection is justified and supported by the safety and tolerability profile of the regimen in AMD and DME studies. Furthermore, IVT injection permits direct targeting of VTE to the retina and is associated with only low systemic plasma concentrations that are unlikely to have significant systemic effects.

## Efficacy

### Overview

The submission included two completed, pivotal, Phase III, randomised, double-masked, and sham-controlled efficacy and safety studies provided to support the registration of Eylea for the treatment of macular oedema secondary to CRVO: Study VGFT-OD-0819 (COPERNICUS) and Study 14130 (GALILEO). The studies included a total of 366 randomised patients. In both studies, the primary efficacy endpoint was the proportion of subjects who gained ≥ 15 letters of best corrected visual acuity (BCVA) at Week 24. The primary efficacy endpoint was compared in subjects treated with sham injections and subjects treated with VTE 2 mg via intravitreal (IVT) injections every 4 weeks (VTE2Q4) from Week 0 to Week 20. In both studies, only 1 eye was treated and designated as the study eye, the other eye was designated the fellow eye.

In COPERNICUS, after the first 24 weeks of treatment subjects in both the sham and VTE2Q4 groups were eligible for VTE injections administered as needed (PRN) through to Week 100. In GALILEO, after the first 24 weeks of treatment subjects in the VTE2Q4 group were eligible for VTE injections PRN through to Week 76, while subjects in the sham group continued with sham every 4 weeks through to Week 52 after which they became eligible for VTE PRN through to Week 76.

### Evaluator's conclusions on clinical efficacy

It is considered that the submitted data have satisfactorily established the efficacy of Eylea for the treatment of CRVO secondary to macular oedema. However, there is a significant issue relating to the most appropriate treatment regimen to be adopted after the first 6 months of VTE2Q4 treatment. In both COPERNICUS and GALILEO, subjects initially

randomised to VTE2Q4 were switched to VTE PRN from Week 24. The VTE PRN phase ran from Week 24 to Week 100 in COPERNICUS and from Week 24 to Week 76 in GALILEO. The sponsor proposes that, following the first 6 months treatment with VTE2Q4, subjects should continue treatment with VTE2Q8 rather than switching to VTE PRN. However, there are no confirmatory data supporting the proposed VTE2Q8 regimen from 6 months onwards. In both COPERNICUS and GALILEO, improvements in BCVA at Week 24 were largely maintained through to Week 52 following switching to VTE PRN based on monthly assessment for re treatment.

In COPERNICUS, 56.1% (64/114) of subjects in the VTE2Q4 group gained 15 or more letters at Week 24 compared with 12.3% (9/73) of subjects in the sham group, with the adjusted difference between the two groups being 44.8% (95% CI: 33.0, 56.6), p<0.0001. In the primary efficacy analysis, subjects who discontinued before Week 24 with < 5 injections were assessed as failures (otherwise last observation carried forward (LOCF)). Two sensitivity analyses of the primary efficacy endpoint both supported the results observed for the primary efficacy analysis. One of the sensitivity analyses assessed all subjects discontinued before Week 24 as treatment failures and the other sensitivity analysis used the LOCF method to impute missing values.

In GALILEO, 60.2% (62/103) of subjects in the VTE2Q4 group gained 15 or more letters at Week 24 compared with 22.1% (15/68) in the sham group, with the adjusted difference between the two groups being 38.3% (95% CI: 24.4, 52.1), p<0.0001. In the primary efficacy analysis, subjects who discontinued before Week 24 were all assessed as treatment failures. Two sensitivity analyses of the primary efficacy endpoint in GALILEO both supported the results observed for the primary efficacy analysis. One of the sensitivity analyses assessed subjects discontinued before Week 24 with < 5 injections as failures (otherwise LOCF) and the other sensitivity analysis used the LOCF method to impute missing values.

In COPERNICUS, the results for all four secondary efficacy endpoints at Week 24 (analysed in a pre-specified hierarchical manner to account for multiplicity) clinically and statistically significantly favoured VTE2Q4 compared with sham (that is, change from baseline in BCVA score, change from baseline in CRT, progression to any neovascularisation and change from baseline in the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score). The results for the secondary efficacy analyses fully support the primary efficacy analysis showing that treatment with VTE2Q4 for 24 weeks is superior to sham.

In GALILEO, there were five secondary efficacy endpoints at Week 24 and clinically and statistically significant differences in favour of VTE2Q4 compared with sham were seen for the first two endpoints tested using the pre-specified hierarchical sequence (that is, change from baseline in BCVA score and change from baseline in CRT). However, as there was no statistically significant difference between the two treatments for the third sequential secondary efficacy endpoint (progression to any neovascularisation) hypothesis testing was stopped. Therefore, for the sequential fourth and fifth secondary efficacy endpoints, the p values for the comparisons between the two treatment groups were nominal rather than confirmatory (that is, changes from baseline in the NEI VFQ-25 total score [fourth endpoint] and the EQ-5D [15] total score [fifth endpoint]). The results for the secondary efficacy analyses partially support the primary efficacy analysis showing that treatment with VTE2Q4 for 24 weeks is superior to sham.

In both COPERNICUS and GALILEO, efficacy was assessed at Week 52 following a VTE PRN phase from Week 24 to Week 52, and efficacy was also assessed at Week 100 in COPERNICUS following a further VTE PRN extension phase from Week 52 to Week 100,

[15] EQ-5D™ is a standardised instrument for use as a measure of health outcome.

and at Week 76 in GALILEO following a further PRN extension phase from Week 52 to Week 76. In both studies, efficacy endpoints assessed at time points after Week 24 were defined as tertiary efficacy endpoints and were considered to be exploratory rather than confirmatory, with all p values for pair wise comparisons being nominal (descriptive). No statistical adjustments were made for multiplicity of testing of tertiary efficacy endpoints.

In COPERNICUS, from Week 24 through to Week 48 subjects in both the VTE and sham groups were assessed monthly to receive either VTE PRN or sham according to pre-specified re treatment criteria. Starting at Week 52, all subjects were eligible to continue in a one year PRN extension during which they were evaluated every quarterly to receive open label VTE according to pre specified re treatment criteria. However, if in the investigator's opinion a subject required more frequent VTE dosing than quarterly in the Week 52 to Week 100 PRN phase then VTE injections may have been given as frequently as every 4 weeks.

In COPERNICUS, comparisons between the sham + VTE PRN and VTE2Q4+PRN treatment groups after Week 24 are confounded by the presence of subjects treated with VTE in the sham + VTE PRN group. Of the 60 subjects in the sham treatment group who completed Week 24 and were eligible to receive VTE after Week 24, 57 (95%) subjects crossed-over to receive at least one VTE PRN injection through to Week 100. The mean (standard deviation (SD)) number of VTE injections received by subjects in the sham + VTE PRN group from baseline to Week 100 was 6.4 (3.72), with a median of 7.0 injections and a range of 0 to 15 injections. Of the 110 subjects in the VTE2Q4 group who completed Week 24 and were eligible to receive VTE PRN after Week 24, 106 (96.4%) subjects received at least one VTE PRN injection through to Week 100. The mean (SD) number of VTE injection received by subjects in the VTE2Q4+PRN group from baseline to Week 100 was 11.8 (3.35), with a median of 11.5 injections and a range of 4 to 21 injections. In the Week 24 to Week 100 PRN phase, 80% (n=48) of subjects in the sham + VTE PRN group and 29.1% (n=32) of subjects in the VTE2Q4+PRN group received a VTE PRN injection at the first eligible time point (that is, at Week 24). The mean (SD) time to first injection in the Week 24 to Week 100 PRN phase was shorter in the sham + VTE PRN group than in the VTE2Q4+PRN group (54.5 [98.57] days versus 92.8 [98.78] days).

The results (COPERNICUS) for the proportion of subjects who gained at least 15 letters in BCVA at Weeks 24, 52 and 100 are summarised below in Table 2. The results show that the proportion of subjects in the VTE2Q4+PRN group who gained at least 15 letters from baseline was similar at Week 24 (56.1%) and Week 52 (55.3%) but had fallen by 7% from Week 24 at Week 100 (49.1%).

**Table 2: COPERNICUS – Proportion of subjects who gained at least 15 letters at Weeks 24, 52, and 100; Full Analysis Set (FAS)/subjects who discontinued prior to Week 24 with < 5 injections of VTE or sham were evaluated as non-responders, otherwise missing values were imputed using LOCF.**

| | Sham+PRN (N=73) | VEGF Trap-Eye 2Q4+PRN (N=114) |
|---|---|---|
| Subjects who Gained at Least 15 Letters in BCVA at Week 24, n (%) | 9 (12.3) | 64 (56.1) |
| Difference (%) | | 43.8 |
| Adjusted Difference (%) (95% CI) [1] | | 44.8 (33.0, 56.6) |
| P-value [2] | | <0.001 |
| Subjects who Gained at Least 15 Letters in BCVA at Week 52, n (%) | 22 (30.1) | 63 (55.3) |
| Difference (%) | | 25.1 |
| Adjusted Difference (%) (95% CI) [1] | | 25.9 (11.8, 40.1) |
| P-value [2] | | <0.001 |
| Subjects who Gained at Least 15 Letters in BCVA at Week 100, n (%) | 17 (23.3) | 56 (49.1) |
| Difference (%) | | 25.8 |
| Adjusted Difference (%) (95% CI) [1] | | 26.7 (13.1, 40.3) |
| P-value [2] | | 0.0003 |

[1] = Adjusted difference (VEGF Trap-Eye 2Q4+PRN minus Sham+PRN) and associated 95% CI were calculated using the CMH weighting scheme adjusted by regions (North America versus Rest of World) and baseline BCVA (BCVA >20/200 and BCVA ≤20/200). [2] = P-value was calculated using 2-sided CMH test adjusted by regions (North America versus Rest of World) and baseline BCVA (BCVA >20/200 and BCVA ≤20/200). The Week 24 result was the primary efficacy endpoint, while the Week 52 and 100 results were tertiary efficacy endpoints and p values at these two time-points were provided for descriptive (exploratory) purposes only.

The results (COPERNICUS) for the BCVA as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Weeks 24, 52 and 100 are summarised below in Table 3. The results show that subjects in the VTE2Q4+PRN group had a mean improvement from baseline to Week 24 of 17.3 letters (3.5 lines). At Week 52, the mean BCVA letter score had fallen by 1.2 letters from Week 24 (that is, from 68.0 [Week 24] to 66.8 [Week 52]), and at Week 100 the mean BCVA letter score had fallen further from Week 24 by 4.3 letters (that is, from 68.0 [Week 24] to 63.6 [Week 100]).

**Table 3: COPERNICUS – Change from baseline to Weeks 24, 52, and 100 in BCVA score using ETDRS; FAS/LOCF.**

| | n | Baseline Mean | Endpoint Mean | Mean Change | LS Mean Change | Difference (95% CI [1]) | P-value [2] |
|---|---|---|---|---|---|---|---|
| Treatment (Week 24) | | | | | | 21.70 (17.36, 26.04) | <0.001 |
| Sham (N=73) | 73 | 48.9 | 44.8 | -4.0 | -5.33 | | |
| VEGF Trap-Eye 2Q4 (N=114) | 114 | 50.7 | 68.0 | 17.3 | 16.36 | | |
| Treatment (Week 52) | | | | | | 12.71 (7.69, 17.74) | <0.001 |
| Sham+PRN (N=73) | 73 | 48.9 | 52.7 | 3.8 | 1.30 | | |
| VEGF Trap-Eye 2Q4+PRN (N=114) | 114 | 50.7 | 66.8 | 16.2 | 14.01 | | |
| Treatment (Week 100) | | | | | | 11.81 (6.65, 16.79) | <0.0001 |
| Sham+PRN (N=73) | 73 | 48.9 | 50.4 | 1.5 | -0.20 | | |
| VEGF Trap-Eye 2Q4+PRN (N=114) | 114 | 50.7 | 63.6 | 13.0 | 11.6 | | |

[1] = Point estimate and 95% CI are based on treatment difference (VEGF Trap-Eye 2Q4+PRN minus Sham+PRN) of LS mean changes using an ANCOVA model with treatment group, region and baseline BCVA (> 20/200 and ≤ 20/200) as fixed factors. [2] = P-value is based on treatment difference (VEGF Trap-Eye 2Q4+PRN minus Sham+PRN) of the LS mean changes using an ANCOVA model with treatment group, region and baseline BCVA (> 20/200 and ≤ 20/200) as fixed factors. The Week 24 result was for a pre-specified secondary efficacy endpoint, while the Week 52 and 100 results were for tertiary efficacy endpoints and the p values were provided for descriptive (exploratory) purposes only.

The results (COPERNICUS) for the change in CRT from baseline as measured by OCT at weeks 24, 52, and 100 are summarised below in Table 4. The results show that maximum reduction in the mean CRT from baseline in subjects in the VTE2Q4+PRN group occurred at Week 24 with mean values at Week 52 and Week 100 increasing by 44 µm and 67 µm, respectively, from Week 24.

**Table 4: COPERNICUS – Change from baseline to Weeks 24, 52 and 100 in CRT (µm); FAS/LOCF**

| | n | Baseline Mean | Endpoint Mean | Mean Change | LS Mean Change | Difference (95% CI [1]) | P-value [2] |
|---|---|---|---|---|---|---|---|
| Treatment (Week 24) | | | | | | -311.9 (-389.4, -234.4) | <.001 |
| Sham (N=73) | 65 | 664.0 | 519.2 | -144.8 | -175.2 | | |
| VEGF Trap-Eye 2Q4 (N=114) | 112 | 661.7 | 204.5 | -457.2 | -487.1 | | |
| Treatment (Week 52) | | | | | | -28.44 (-121.2, 64.34) | 0.546 |
| Sham+PRN (N=73) | 65 | 664.0 | 282.2 | -381.8 | -426.7 | | |
| VEGF Trap-Eye 2Q4+PRN (N=114) | 112 | 661.7 | 248.7 | -413.0 | -455.1 | | |
| Treatment (Week 100) | | | | | | -44.63 (-141.8, 52.58) | 0.3661 |
| Sham+PRN (N=73) | 65 | 664.0 | 320.7 | -386.8 | -343.3 | | |
| VEGF Trap-Eye 2Q4+PRN (N=114) | 112 | 661.7 | 271.7 | -431.4 | -390.0 | | |

[1] and [2] information is consistent with that above for Table 3.

In COPERNICUS, the proportion of subjects who developed any neovascularisation from baseline to Week 100 was greater in the sham + VTE PRN group (11.0% [8/73]) than in the VTEQ24+PRN group (5.3% [6/114]) but the difference between the two treatment groups was not statistically significant (p=0.1810). Pan-retinal photocoagulation was performed in 4 (5.5%) subjects in the sham + VTE PRN group and no subjects in the VTE2Q4+PRN group.

In GALILEO, from Week 24 to Week 48 subjects in the VTE2Q4+PRN group received either VTE or sham PRN injections monthly depending on pre specified re treatment criteria, while subjects in the sham group continued with monthly sham injections (that is, no switching to VTE). Beginning at Week 52, all subjects were eligible to receive VTE PRN injections based on the pre specified re treatment criteria (in order to maintain masking, sham injections were given if the re treatment criteria were not met) and were evaluated every 8 weeks (Week 60 and Week 68).

In GALILEO, over the 76 weeks of treatment the total mean (SD) exposure to VTE was 18.3 (6.4) mg in the VTE2Q4+PRN group (n=104), with a median of 19.0 mg and a range of 2 to 30 mg, and 2.5 (2.3) mg in the sham + VTE PRN group (n=68), with a median of 2.0 mg and a range of 0 to 6 mg. The comparison between the two treatment groups at Week 52 involved subjects who had been treated with VTE2Q4+PRN or sham from Week 0 and was not potentially confounded by subjects in the sham group who had crossed over to VTE PRN. However, the comparison between the two treatment groups at Week 76 was confounded by the presence of subjects in the sham group who had crossed-over to VTE injections at some point from Week 52 to Week 68.

The results (GALILEO) for the proportion of subjects who gained at least 15 letters from baseline at Week 24, 52 or 76 are summarised below in Table 5. The results show a reduction in the proportion of subjects who achieved a gain of at least 15 letters from baseline at Week 52 (58.3%) and Week 76 (55.3%) compared with Week 24 (60.2%).

**Table 5: GALILEO - Proportion of subjects who gained at least 15 letters at Weeks 24, 52, and 76; FAS/discontinued subjects before Week 24 judged as treatment failures.**

| | Sham+VTE PRN[d] N=68 | VTE2Q4+PRN[d] N=103 |
|---|---|---|
| **Week 24 Results** | | |
| No (%) of subjects who gained ≥15 letters from baseline at Week 24 | 15 (22.1) | 62 (60.2) |
| Difference[a] (%) | | 38.1 |
| CMH adjusted difference[a,b] (%) (95% CI) | | 38.3 (24.4, 52.1) |
| p-value[c] | | < 0.0001 |
| Source: CSR A52377 In-Text Table 23 | | |
| **Week 52 Results** | | |
| No (%) of subjects who gained ≥15 letters from baseline at Week 52 | 22 (32.4) | 60 (58.3) |
| Difference[a] (%) | | 25.9 |
| CMH adjusted difference[a,b] (%) (95% CI) | | 25.9 (11.1, 40.8) |
| p-value[c] | | 0.0010 |
| Source: CSR A59664 In-Text Table 50 | | |
| **Week 76 Results** | | |
| No (%) of subjects who gained ≥15 letters from baseline at Week 76 | 20 (29.4) | 57 (55.3) |
| Difference[a] (%) | | 25.9 |
| CMH adjusted difference[a,b] (%) (95% CI) | | 26.0 (11.4, 40.7) |
| p-value[c] | | 0.0009 |
| Source: Post-text Table 14.2.1/11 | | |

a: difference is VTE2Q4+PRN minus sham+VTE PRN
b: estimate and CI are calculated using CMH weights adjusted for region (Europe vs. Asia/Pacific) and baseline BCVA category (> 20/200 vs ≤ 20/200)
c: p-value is calculated using 2-sided CMH-test adjusted by region and baseline BCVA category
d: VTE2Q4+PRN: Week 0-Week 20 VTE2Q4, Week 24-Week 48 VTE2Q4 PRN, Week 52-Week 68 PRN every 8 weeks; sham+VTE PRN: Week0-Week 48 sham, Week 52 VTE (or sham), Week 60-Week 68 VTE PRN every 8 weeks

The results (GALILEO) for the BCVA as measured by the ETDRS letter score at Weeks 24, 52, and 76 are summarised below in Table 6. The results show that subjects in the VTE2Q4 group had a mean improvement from baseline to Week 24 of 18.0 letters (3.6 lines). In the VTE2Q4+PRN group, at Week 52 the mean BCVA letter score had fallen by 1.2 letters from Week 24 (that is, from 71.6 [Week 24] to 70.4 [Week 52]), and at Week 76 the mean BCVA letter score had fallen further from Week 24 by 4.3 letters (that is, from 71.6 [Week 24] to 67.3 [Week 76]).

**Table 6: GALILEO – Change from baseline in ETDRS letter score at Weeks 24, 52, and 76; FAS/LOCF.**

| | n | Baseline[a] Mean (SD) | Endpoint[a] Mean (SD) | Mean (SD) Change[a] | LSmean Change | Difference[b] (95% CI) | p[c] |
|---|---|---|---|---|---|---|---|
| **Week 24 Results** | | | | | | | |
| Sham[d] | 68 | 50.9 (15.4) | 54.3 (20.2) | 3.3 (14.1) | 3.0 | 14.7 | <0.0001 |
| VTE2Q4 | 103 | 53.6 (15.8) | 71.6 (17.1) | 18.0 (12.2) | 17.7 | (10.8, 18.7) | |
| Source: CSR A52377 In-Text Table 32 | | | | | | | |
| **Week 52 Results** | | | | | | | |
| Sham[d] | 68 | 50.9 (15.4) | 54.7 (21.8) | 3.8 (18.1) | 4.9 | 13.2 | <0.0001 |
| VTE2Q4+PRN | 103 | 53.6 (15.8) | 70.4 (18.6) | 16.9 (14.8) | 18.1 | (8.2, 18.2) | |
| Source: CSR A59664 In-text Table 36 | | | | | | | |
| **Week 76 Results** | | | | | | | |
| Sham+VTE PRN[d] | 68 | 50.9 (15.4) | 57.1 (21.3) | 6.2 (17.7) | 7.4 | 7.6 | 0.0070 |
| VTE2Q4+PRN | 103 | 53.6 (15.8) | 67.3 (21.4) | 13.7 (17.8) | 15.0 | (2.1, 13.1) | |
| Source: Post-Text Table 14.2.2/1 and Post-text Table 14.2.2/3 | | | | | | | |

a: absolute values
b: Difference in LS mean change. Point estimate and 95% CI are based on treatment difference (VTE2Q4+PRN minus sham+VTE PRN) of the LS mean changes using an ANOVA model with treatment group, region, and baseline BCVA category as fixed factors.
c: p-value is based on treatment difference (VTE2Q4 minus sham+VTE PRN) of the LS mean changes using the model described above.
d: VTE2Q4+PRN: Week 0-Week 20 VTE2Q4, Week 24-Week 48 VTE2Q4 PRN, Week 52-Week 68 PRN every 8 weeks; sham+VTE PRN: Week0-Week 48 sham, Week 52 VTE (or sham), Week 60-Week 68 VTE PRN every 8 weeks

The results (GALILEO) for the change in CRT from baseline as measured by OCT at Weeks 24, 52 and 76 are summarised below in Table 7. Similar to the BCVA endpoints, the results show that maximum reduction in the mean CRT from baseline in subjects in the

VTE2Q4+PRN group occurred at Week 24 (-448.58 µm), with mean values at Week 52 and Week 76 being -423.53 µm and -389.35 µm (that is, CRT increased at Weeks 52 and 76 compared with Week 24).

**Table 7: GALILEO – Change from baseline in CRT at Weeks 24, 52 and 76; FAS/LOCF.**

| | n | Baseline[a] Mean (SD) | Endpoint[a] Mean (SD) | Mean (SD) Change[a] | LS Mean Change | Difference[b] (95% CI) | p value[c] |
|---|---|---|---|---|---|---|---|
| **Week 24 Results** | | | | | | | |
| Sham[d] | 68 | 638.66 (224.69) | 464.89 (205.48) | -169.27 (224.72) | -208.55 | -239.42 | <0.0001 |
| VTE2Q4 | 103 | 683.20 (234.46) | 234.62 (109.27) | -448.58 (256.02) | -447.97 | (-286.31, -192.53) | |
| Source: CSR A52377 In-Text Table 35 | | | | | | | |
| **Week 52 Results** | | | | | | | |
| Sham[d] | 68 | 638.66 (224.69) | 414.90 (202.99) | -219.26 (233.85) | -274.15 | -167.47 | <0.0001 |
| VTE2Q4+PRN | 103 | 683.20 (234.46) | 259.68 (136.39) | -423.53 (250.29) | -441.62 | (-216.62, -118.33) | |
| Source: CSR A59664, In-text Table 52 | | | | | | | |
| **Week 76 Results** | | | | | | | |
| Sham+VTE PRN[d] | 68 | 638.66 (224.69) | 327.79 (191.58) | -306.37 (246.85) | -364.69 | -44.16 | 0.1122 |
| VTE2Q4+PRN | 103 | 683.20 (234.46) | 293.85 (173.01) | -389.35 (273.71) | -408.85 | (-98.76, 10.44) | |
| Source: Post-text Table 14.2.3/1 and Post-text Table 14.2.3/3 | | | | | | | |

a: absolute values
b: Difference in LS mean change. Point estimate and 95% CI are based on treatment difference (VTE2Q4+PRN minus sham+VTE PRN) of the LS mean changes using an ANOVA model with treatment group, region, and baseline BCVA category as fixed factors.
c: p-value is based on treatment difference (VTE2Q4 minus sham+VTE PRN) of the LS mean changes using the model described above.
d: VTE2Q4+PRN: Week 0-Week 20 VTE2Q4, Week 24-Week 48 VTE2Q4 PRN, Week 52-Week 68 PRN every 8 weeks; sham+VTE PRN: Week0-Week 48 sham, Week 52 VTE (or sham), Week 60-Week 68 VTE PRN every 8 weeks

In GALILEO, 7.8% (8/103) of subjects in the VTE2Q4+PRN group and 8.8% (6/68) of subjects in the sham + VTE PRN group developed neovascularisation during the 76 weeks of the study; p=0.8887. Pan-retinal photocoagulation was performed in 1.9% (2/103) of subjects in the VTE2Q4+PRN group and 4.4% (3/68) of subjects in the sham + VTE PRN group.

Overall, in COPERNICUS the BCVA results at Week 52 and Week 100 indicate that the gains in BCVA achieved at Week 24 were maintained to greater extent at Week 52 than at Week 100. These results suggest that more frequent routine monitoring in the Week 24 to Week 52 period (that is, every 4 weeks) than in the Week 52 to Week 100 period (that is, every 12 weeks) is associated with better outcomes. In the Week 24 to Week 52 period, 91.9% (100/110) of subjects in the VTE2Q4+PRN group received at least one VTE PRN injection and 29.1% (32/110) of the subjects received a VTE PRN injection at the first eligible PRN injection time-point at Week 24. The mean (SD) number of VTE PRN injections in the VTE2Q4+PRN group (n=110) was 2.7 (1.7), with a median of 3.0 injections and a range of 0 to 7 injections. The first injection in the Week 24 to Week 52 PRN extension phase could be given and Week 24 and the last at Week 48. Therefore, over the 24 week period in which VTE PRN injections could be administered, approximately 3 injections were given resulting, on average, 1 injection being given every 8 weeks.

Overall, in GALILEO the BCVA indicate that the gains achieved at Week 24 were maintained to greater extent at Week 52 than at Week 76. These results suggest that more frequent routine monitoring in the Week 24 to Week 52 period (that is, every 4 weeks) than in the Week 52 to Week 76 period (that is, every 8 weeks) is associated with better outcomes. In the Week 24 to Week 52 period, the mean (SD) number of VTE PRN injections administered to subjects in the VTE2Q4+PRN group (n=97) was 2.5 (1.7) with a median of 3.0 injections and a range of 0 to 6 injections. The first injection in the Week 24 to Week 52 extension phase could be given and Week 24 and the last at Week 48. Therefore, over the 24 week period in which VTE PRN injections could be administered, approximately 3 injections were given resulting, on average, in one injection being given every 8 weeks.

In both COPERNICUS and GALILEO, improvements in BCVA achieved at Week 24 following VTE2Q4 were largely maintained through to Week 52 following monthly monitoring and re treatment with VTE PRN according to pre-specified re treatment criteria. In both COPERNICUS and GALILEO, the proportion of subjects who had gained at least 15 letters in the ETDRS from baseline was lower at Week 52 than at Week 24 by 0.8% and 1.9%, respectively, while in both studies the mean BCVA was 1.2 letters lower at Week 52 than

at Week 24. In both COPERNICUS and GALILEO, the mean CRT increased from Week 24 to Week 52 by approximately 43 µm and 25 µm, respectively but the increases in thickness did not appear to significantly reduce BCVA.

The sponsor acknowledged that although the deterioration of the disease at the end of the Week 24 to Week 52 PRN dosing phase "*may be rather minor after only 6 months [of PRN dosing] it is likely to become more significant over the expected long-term treatment duration needed by patients with CRVO. These data, therefore, support the recommendation that patients be treated according to a consistent, proactive dosing regimen rather than a reactive dosing regimen that is based on deterioration in visual and/or morphology endpoints, where a complete recovery might not always be possible*".

The difficulty with sponsor's recommendation supporting the proactive VTE2Q8 regimen from 6 months onwards is that that there are no confirmatory studies supporting the proposed treatment regimen. The available data from COPERNICUS and GALILEO indicate that clinically meaningful improvements in BCVA achieved at Week 24 after VTE2Q4 treatment can be largely maintained for at least 6 months with a VTE PRN regimen based on monthly assessment and adherence to pre-specified re treatment criteria. Therefore, based on efficacy outcomes alone it is considered that the data in the sponsor's "Justification for posology" document do not support the proposed VTE2Q8 regimen from 6 months onwards. However, as discussed later in this CER, the incidence of CRVO disease-related treatment emergent adverse events (TEAEs) increases following switching from proactive VTE2Q4 from Week 0 to Week 24 to reactive VTE PRN from Week 24 to Week 52 providing support to a proactive regimen rather than a PRN regimen from Week 24 onwards.

## Safety

### Studies providing evaluable safety data

The relevant data supporting the safety of Eylea (VTE) for the treatment of CRVO were provided in two, completed, pivotal, Phase III studies (COPERNICUS [Week 0 to Week 100] and GALILEO [Week 0 to Week 76]). In addition to the safety data provided in the two individual study reports, the submission also included an integrated summary of the safety data from both studies from baseline through to Week 52 in three cuts (Weeks 0 to 24; Weeks 24 to 52; and Weeks 0 to 52). The date of the first visit for the first subject in either study was 08 July 2009, and the date of the last Week 52 visit for the last subject in either study was 13 May 2011. The integrated summary of the safety data has been evaluated as have the Week 0 to Week 76 safety data from GALILEO and the Week 0 to Week 100 safety data from COPERNICUS. The safety data referred to in the CER relate to the relevant safety analyses sets (SAFs) unless otherwise stated.

In both COPERNICUS and GALILEO, safety assessments included ophthalmic examinations, recording and evaluation of clinical AEs, safety laboratory measurements, vital signs and immunogenicity. AE information was collected at each study visit throughout the study, regardless of whether the event was attributed to study treatment or procedures. AEs were collected up to 30 days after the last dose of the study drug or the early termination visit, whichever was the later. Standard International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) definitions were used for AEs and serious AEs (SAEs). In addition to standard AE and SAE reporting criteria, the studies also included satisfactory criteria for reporting serious (sight-threatening) ocular adverse events. Assessment of the causal relationship between an AE and the administration of treatment was made by the relevant investigator (that is,

reasonable causal relationship, yes or no). The studies included reporting of pre specified treatment emergent ocular and non ocular AEs of special interest.

### Postmarketing experience

No postmarketing experience relating to Eylea for the treatment of CRVO was submitted. However, the medicine has only recently been approved in the USA for this indication. The sponsor's Summary of Clinical Safety included a statement indicating that the Core Company Safety Document (CCSD) has been updated to include adverse drug reactions "*pertaining to intraocular inflammation (anterior chamber flare, iridocyclitis, iritis, uveitis, vitritis, and hypopyon) ..... to reflect the to-date postmarketing experience in the AMD indication". The summary stated that "no other postmarketing data relevant to the CRVO indication have been identified at this time*".

### Evaluator's overall conclusions on clinical safety

The evidence supporting the safety of VTE for the treatment of CRVO is derived from the integrated safety analysis of COPERNICUS and GALILE0 (Weeks 0-24, 24-52 and 0-52), and the long-term data from COPERNICUS (Weeks 0 to 100) and GALILEO (Weeks 0 to 76). The Week 0 to Week 52 safety data from the integrated analysis included a total of 275 subjects treated with at least one dose of VTE (218 subjects in the combined VTE2Q4+PRN group plus 57 subjects in the COPERNICUS sham + VTE PRN group who had switched to VTE from Week 24 to Week 52). In COPERNICUS, 169 subjects received at least one dose of VTE from Week 0 to Week 100, and in GALILEO 146 subjects received at least one dose of VTE from Week 0 to Week 76.

Overall, the submitted data showed that VTE for the treatment of CRVO was generally well tolerated and displayed a satisfactory safety profile for up to 100 weeks of treatment. The major safety issue relates to the increased incidence of macular oedema and other common CRVO disease related TEAEs observed in subjects switched from monthly proactive treatment to reactive PRN treatment from Week 24 based on pre specified re treatment criteria. The following safety summary focuses on the Week 0 to Week 24 period for the two, pivotal, Phase III studies (COPERNICUS and GALILEO), the Week 0 to Week 100 period for COPERNICUS, the Week 0 to 76 period for GALILEO and the safety issues associated with switching from proactive to reactive VTE treatment from Week 24 onwards.

### Week 0 to Week 24 – integrated analysis (SAF)

In the integrated analysis of the Week 0 to Week 24 safety data the majority of subjects in the sham and VTE2Q4 groups reported at least one TEAE: 115/142 (80.9%) sham; 166/218 (76.1%) VTE2Q4. The proportion of subjects discontinuing the study drug before Week 24 was notably higher in the sham group than in the VTE2Q4 group (20.4% [n=29] versus 6.4% [n=14], respectively). The proportion of subjects discontinuing the study drug due to TEAEs was higher in the sham group (7.0% [10/142]) than in the VTE2Q4 group (1.4% [3/218]. TEAEs resulting in discontinuation of the study drug in 2 or more subjects were vitreous haemorrhage in the VTE2Q4 group (2 [2.7%], VTE2Q4 versus 0 [0]%, sham) and retinal neovascularisation in the sham group (3 [4.4%], sham versus 0 [0%] VTE2Q4). All other TEAEs resulting in discontinuation of the study drug each occurred in 1 patient only in either treatment group.

The incidence of ocular TEAEs in the study eye was higher in the sham group (94 subjects [66.2%]) than in the VTE2Q4 group (129 subjects [59.2%]). The highest incidence of ocular TEAEs occurred in subjects in the sham/COPERNICUS group (67.6%) followed by the sham/GALILEO group (64.7%) and the VTE2Q4 group (59.2%). Commonly occurring

ocular TEAEs in the study eye reported more frequently in subjects in the VTE2Q4 group than in subjects in both the sham/GALILEO and sham/COPERNICUS groups were (respectively): eye pain (12.8% versus 4.4% versus 5.4%); macular fibrosis (4.1% versus 1.5% versus 1.4%); optic disc vascular disorder (6.0% versus 4.4% versus 1.4%); and vitreous floaters (5.0% versus 0% versus 2.7%). Macular oedema occurred notably more commonly in the sham/GALILEO (16.2%) group than in the sham/COPERNICUS and the VTE2Q4 groups (1.4% in each group).

The incidence of serious ocular TEAEs in the study eye was higher in the sham group (15 subjects [10.6%]) than in the VTE2Q4 group (6 subjects [2.8%]). Most serious ocular TEAEs in the study eye were attributable to disease progression or the injection procedure. Serious ocular TEAEs in the study eye reported in 2 or more subjects occurred only in the sham group. One (1) subject (0.5%) in the VTE2Q4 group experienced an SAE of endophthalmitis compared with no subjects in the sham group. There were no reports of SAEs of macular oedema in the VTE2Q4 group, while 2 subjects (1.4%) in the sham group experienced this event. There were 2 deaths, both of which occurred in COPERNICUS in patients treated with sham and both of which were adjudicated as Arterial thromboembolic events (ATE)/Antiplatelets Trialist's Collaboration (APTC) events (PTs: 1 acute myocardial infarction; 1 arrhythmia).

Ocular injection related TEAEs in the study eye most frequently occurred in subjects in the VTE2Q4 group (31.2% [68/218]) than in the sham group (22.5% [32/142]). The most commonly reported ocular injection related TEAEs occurring in ≥ 2% more subjects in the VTE2Q4 group than in the sham group were eye pain (11.0% versus 3.5%) and intraocular pressure (IOP) increased (5.5% versus 1.4%).

The overall incidence of ocular TEAEs of interest in the study eye was higher in subjects in the sham group (51/142 [35.9%]) than in the VTE2Q4 group (64/218 [29.4%]). The most common ocular TEAEs of interest (≥ 5% overall) in subjects in the VTE2Q4 group were: subconjunctival/conjunctival haemorrhage (26 [11.9%], VTE2Q4 versus 24 [19.4%], sham); mild transient pain at the injection site (26 [11.9%], VTE2Q4 versus 7 [4.9%], sham); transient increase in IOP (13 [6.0%], VTE2Q4 versus 2 [1.4%], sham); and clinically significant decrease in BCVA (13 [6.0%], VTE2Q4 versus 23 [16.2%], sham). The only common ocular TEAEs of interest (≥ 5%) in the study eye in subjects in the VTE2Q4 group with an incidence of more than twice that in the sham group was mild transient pain at the injection site (26 [11.9%], VTE2Q4 versus 7 [4.9%], sham). The only common ocular TEAEs of interest (≥ 5%) in the study eye in subjects in the sham group with an incidence more than twice that in the VTE2Q4 group was clinically significant decrease in BCVA (23 [16.2%], sham versus 13 [6.0%], VTE2Q4). Two (2) subjects (1.4%) in the sham group experienced IOP ≥ 35 mmHg that required treatment (versus no subjects in the VTE2Q4 group); 9 subjects experienced new onset, elevated IOP that required treatment (6 [4.2%], sham versus 3 [1.4%], VTE2Q4); and 15 subjects experienced transient increases in IOP (2 [1.4%], sham versus 13 [6.0%], VTE2Q4).

Post hoc adjudication of ATE/APTC events was performed by masked adjudicators. In COPERNICUS, there were no ATE/APTC events in the VTE2Q4 group during the first 24 weeks of treatment, while 2 subjects in the sham group experienced ATE/APTC events (PTs: 1 acute myocardial infarction resulting in death; 1 arrhythmia resulting in death). In GALILEO, no potential ATEs during the first 24 weeks of treatment were adjudicated as APTC events.

The proportion of subjects with at least one non ocular TEAE was higher in subjects in the sham/GALILEO group (54.4% [37/68]) than in both the sham/COPERNICUS (51.4% [38/74]) and the VTE2Q4 (48.6% [106/218]) groups. The most common non ocular TEAE in subjects in both the sham and VTE2Q4 groups was nasopharyngitis (10 [7.0%] versus 13 [6.0%], respectively), followed by hypertension (7 [4.9%] versus 14 [6.4%]). The

incidence of serious non ocular TEAEs was higher in subjects in the sham group than in the VTE2Q4 group (11 [7.7%] versus 12 [5.5%], respectively). Pneumonia was the only serious non ocular TEAEs that was reported by more than 1 subject (sham group only, 2 subjects [1.4%]). Non ocular TEAEs of interest occurred in the same proportion of subjects in the sham and VTE2Q4 groups (13 [9.2%] versus 20 [9.2%], respectively). The only notable difference between the two groups was the higher incidence of hypertension in the VTE2Q4 group compared with the sham group (14 [6.4%] versus 7 [4.9%], respectively).

There were no clinically significant changes in laboratory tests (haematology, clinical chemistry or urinalysis) or vital signs in either the sham or the VTE2Q4 group from Week 0 to Week 24.

**Long-term safety (SAF) – Week 0 to 100 (COPERNICUS) and Week 0 to 76 (GALILEO)**

In COPERNICUS, of the 60 subjects in the sham group who completed Week 24, 57 (95.0%) subjects crossed over to receive VTE PRN injections through to Week 100. In the sham + VTE PRN group, in the 60 subjects who completed Week 24 the total number of VTE injections received from baseline to Week 100 was 384 (that is, mean [SD] = 6.4 injections/subject), and in the 110 subjects in the VTE2Q4+PRN group who completed Week 24 the total number of VTE injections received from baseline to Week 100 was 1293 (that is, mean [SD] = 11.8 [3.35] injections/subject).

In GALILEO, of the 52 subjects in the sham group who completed Week 52, 42 (80.8%) subjects received 1 to 3 VTE PRN injections (total 86 injections) from Week 52 to Week 76 (that is, mean [SD] = 1.7 [1.1] injections/subject). VTE injections administered from Week 52 to Week 76 to subjects in the sham + VTE PRN group in GALILEO were the only active injections administered to this group as prior to Week 52 all subjects in this group received only sham injections. In the 91 subjects in the VTE+PRN group who completed Week 52, 63 (69.2%) subjects received 1-3 injections (total 121 injections from Week 52 to Week 76 (that is, mean [SD] = 1.3 [1.1] injections/subject).

In COPERNICUS, nearly all subjects in the sham + VTE PRN group and the VTE2Q4+VTE group experienced at least 1 TEAE over the 100 weeks of the study (70/74 [94.6%] versus 112/114 [98.2%], respectively). The incidence of ocular and non ocular TEAEs leading to withdrawal from the study drug was higher in subjects in the sham + VTE group (5 [6.8%]; all ocular) than in the VTE 2Q4+PRN group (4 [3.5%]; 2 ocular and 2 non ocular). In the VTE2Q4+PRN group, the 2 ocular TEAEs leading to discontinuation of the study drug were retinal artery occlusion (1 [0.9%], VTE2Q4+PRN versus 0 [0%], sham + VTE PRN), and retinal vein occlusion (1 [0.9%], VTE2Q4+PRN versus 0 [0%], sham + VTE PRN). The non ocular TEAEs leading to discontinuation of the study drug in the 2 subjects in the VTE2Q4+PRN group were metastatic renal cell carcinoma (1 [0.9%]) and non-small cell lung cancer (1 [0.9%]).

In GALILEO, the majority of subjects in the sham + VTE PRN group and the VTE2Q4+VTE group experienced at least 1 TEAE over the 76 weeks of the study (61/68 [89.7%] versus 91/104 [87.5%], respectively). The incidence of TEAEs leading to discontinuation of the study drug was higher in subjects in the sham + VTE PRN group than in the VTE2Q4+PRN group (7 [10.3%] versus 7 [6.7%], respectively). In the VTE2Q4+PRN group (versus sham + VTE PRN), the only TEAE occurring in more than 1 subject and leading to discontinuation of the study drug was iris neovascularisation (2 [1.9%] versus 0 [0%], respectively). In the sham + VTE PRN group (versus VTE2Q4+PRN), the three TEAEs leading to discontinuation of the study drug each occurring in more than 1 subject were macular oedema (2 [2.9%] versus 1 [1.0%]), retinal neovascularisation (3 [4.4%] versus 0 [1.0%]) and glaucoma (2 [2.9%] versus 0 [0%]). The only non ocular TEAE leading to

discontinuation of the study drug was hepatic function abnormal in 1 subject (1.0%) in the VTE2Q4+PRN group.

In COPERNICUS, the incidence of ocular TEAEs in the study eye was similar in subjects in both treatment groups over the 100 weeks of the study (63/74 [85.1%], sham + VTE PRN versus 100/114 [87.7%], VTE2Q4+PRN]). Ocular TEAEs occurring in ≥ 5% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: macular oedema (18.4% versus 4.1%); eye pain (18.4% versus 9.5%); retinal vascular disorder (12.3% versus 9.5%); cystoid macular oedema (13.2% versus 6.8%); optic disc vascular disorder (12.3% versus 8.1%); macular fibrosis (10.5% versus 8.1%); retinal exudates (11.4% versus 6.8%); eye irritation (7.9% versus 5.4%); vitreous floaters (7.9% versus 5.4%); cataract (7.0% versus 4.1%); maculopathy (6.1% versus 2.7%); and ocular hyperaemia (5.3% versus 0%). Of particular note was the increased incidence of macular oedema in subjects in the VTE2Q4+PRN group (21 [18.4%]) compared with the sham + VTE PRN group (3 [4.1%]) and the similar proportion of subjects with visual acuity reduced (20 [27.0%] versus 32 [28.1%], respectively). Cystoid macular oedema also occurred more frequently in subjects in the VTE2Q4+PRN group than in the sham + VTE PRN group.

In GALILEO, the incidence of ocular TEAEs in the study eye was similar in subjects in both treatment groups over the 76 weeks of the study (51/68 [75.0%], sham + VTE PRN versus 82/104 [78.8%], VTE2Q4+PRN]). Ocular TEAEs occurring in ≥ 5% of subjects in the VTE2Q4+VTE group and in ≥ 2% more subjects than in the sham + VTE PRN group were: macular oedema (39.4% versus 25.0%); intraocular pressure increased (17.3% versus 5.9%); conjunctival haemorrhage (17.3% versus 7.4%); retinal haemorrhage (15.4% versus 11.8%); eye pain (14.4% versus 5.9%); ocular hyperaemia (8.7% versus 5.9%); vitreous detachment (6.7% versus 1.5%); vitreous floaters (6.7% versus 1.5%); iris neovascularisation (6.7% versus 0%); retinal vein occlusion (6.7% versus 0%); cystoid macular oedema (5.8% versus 1.5%); and injection site pain (5.8% versus 2.9%). Of particular note was the increased incidence of macular oedema in subjects in the VTE2Q4+PRN group (41 [39.4%]) compared with the sham + VTE group (17 [25.0%]) and the similar proportion of patients with visual acuity reduced in both treatment groups (15 [14.4%] versus 9 [13.2%], respectively). Cystoid macular oedema occurred more frequently in subjects in the VTE2Q4+PRN group than in the sham + VTE PRN group, while vitreous haemorrhage occurred in a similar proportion of subjects in both treatment groups.

In COPERNICUS, the incidence of injection related TEAEs in the study eye over the 100 weeks of the study was higher in subjects in the sham + VTE PRN group (21/74 [28.4%]) than in the VTE2Q4+PRN group (45/114 [39.5%]). Injection-related TEAEs in the study eye occurring in ≥ 2% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: eye pain (13.2% versus 5.4%); vitreous floaters (4.4% versus 1.4%); ocular hyperaemia (4.4% versus 0%); IOP increased (2.6% versus 0%); punctate keratitis (2.6% versus 0%); and vitreous detachment (2.6% versus 0%). All other injection related TEAEs occurred in a similar proportion of subjects in both treatment groups.

In GALILEO, the incidence of injection related TEAEs in the study eye over the 76 weeks of the study was higher in subjects in the VTE2Q4+PRN group (44/104 [42.3%]) than in the sham + VTE group (27/68 [39.7%]). Injection related TEAEs in the study eye occurring in ≥ 2% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: conjunctival haemorrhage (17.3% versus 7.4%); eye pain (13.5% versus 5.9%); IOP increased (12.5% versus 4.4%); foreign body sensation in eyes (6.7% versus 4.4%); vitreous floaters (3.8% versus 1.5%); and ocular hypertension (2.9% versus

0%). All other injection related TEAEs occurred in a similar proportion of subjects in both treatment groups.

In COPERNICUS, ocular TEAE of interest in the study eye over the 100 weeks of the study were reported in a similar proportion of subjects in the sham + VTE and VTE2Q4+PRN groups (39 [52.7%] versus 58 [50.9%], respectively). The most commonly reported ocular TEAEs of interest in the study eye (sham + VTE PRN versus VTE2Q4+PRN) occurring in ≥ 10% of all subjects were visual acuity reduced (13.3% versus 25.5%) and conjunctival haemorrhage (13.3% versus 10.0%). Ocular TEAEs of interest in the study eye occurring in ≥ 2% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: eye pain (13.2% versus 5.4%); vitreous floaters (4.4% versus 1.4%); and IOP increased (2.6% versus 0%). The overall incidence of subjects who experienced at least one ocular SAE of interest was low in both treatment groups (1 [1.4%], sham + VTE PRN versus 2 [1.8%], VTE2Q4+PRN). In the sham + VTE PRN group, the SAE was visual acuity reduced, and in the VTE2Q4+PRN group the 2 SAEs were visual acuity reduced and endophthalmitis.

In GALILEO, ocular TEAEs of interest in the study eye over the 76 weeks of the study were reported in a similar proportion of subjects in the VTE2Q4+PRN and sham + VTE PRN groups (45/104 [43.3%] versus 29/68 [42.6%], respectively). The most commonly reported ocular TEAEs of interest in the study eye (sham + VTE PRN versus VTE2Q4+PRN) occurring in ≥ 10% of all subjects were: conjunctival haemorrhage (4.4% versus 16.3%); eye pain (5.9% versus 13.5%); and visual acuity reduced (13.2% versus 14.4%). Ocular TEAEs of interest in the study eye reported in ≥ 2% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: conjunctival haemorrhage (16.3% versus 4.4%); eye pain (13.5% versus 5.9%); IOP increased (12.5% versus 4.4%); visual impairment (4.8% versus 0%); vitreous floaters (3.8% versus 1.5%); and ocular hypertension (2.9% versus 0%).

In COPERNICUS, 4 subjects experienced ATE/APTC events (2 [2.7%], sham + VTE PRN; 2 [1.8%] VTE2Q4+PRN). Two (2) subjects in the sham + VTE group experienced vascular death (PTs of acute MI and arrhythmia), 1 subject in the VTE2Q4+PRN group experienced non fatal MI (PTs of coronary artery stenosis, and MI) and 1 subject in the VTE2Q4+PRN group experienced non fatal stroke (PTs of haemorrhagic cerebral infarction and subarachnoid haemorrhage). In GALILEO, no subjects experienced ATE/APTC events over the 76 weeks of the study.

In COPERNICUS, the incidence of ocular SAEs from baseline to Week 100 in the study eye was about 2 fold higher in the sham + VTE PRN group (12/74 [16.2%]) than in the VTE2Q4+PRN group (10/114 [8.8%]). The most commonly reported ocular SAE in the study eye in the VTE2Q4+PRN group was cataract (3.5% VTE2Q4+PRN versus 1.4% sham + VTE PRN). The only other ocular SAE in the study eye reported in ≥ 1 % of subjects in the VTE2Q4+PRN group and more commonly than in the sham + VTE PRN group was cystoid macular oedema (2 [1.8%] versus 0 [0%]).

In GALILEO, the incidence of ocular SAEs from baseline to Week 76 in the study eye was marginally higher in subjects in the VTE2Q4+PRN group than in the sham + VTE PRN group (11/104 [10.6%]) versus 6/68 [8.8%], respectively). The only ocular SAEs occurring in at least 2 subjects in the VTE2Q4+PRN group (versus sham + VTE PRN) were macular oedema (4 [3.8%] versus 2 [2.9%]) and visual acuity reduced (2 [1.9%] versus 1 [1.5%]). The only ocular SAEs occurring in at least 2 subjects in the sham + VTE PRN group (versus VTE2Q4+PRN) were macular oedema (2 [2.9%] versus 4 [3.8%]) and glaucoma (2 [2.9%] versus 0 [0%]).

In COPERNICUS, the incidence of non ocular TEAEs from baseline to Week 100 was similar in subjects in the sham + VTE PRN and VTR2Q4+PRN groups (60 [81.1%] versus 88 [77.2%]). The only non ocular TEAE reported in ≥ 10% of subjects in the VTE2Q4+PRN

group was hypertension (19.3%, VTE2Q4+PRN versus 16.2%, sham + VTE PRN). Non ocular TEAEs reported in ≥ 5% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: hypertension (19.3% versus 16.2%); nasopharyngitis (8.8% versus 6.8%); upper respiratory tract infection (8.8% versus 5.4%); influenza (7.9% versus 5.4%); bronchitis (6.1% versus 4.1%); sinusitis (6.1% versus 4.1%); urinary tract infection (6.1% versus 4.1%); and anaemia (5.3% versus 2.7%).

In GALILEO, the incidence of non ocular TEAEs from baseline to Week 76 was higher in subjects in the sham + VTE PRN group than in the VTE2Q4+PRN group (50/68 [73.5%] versus 71/104 [68.3%], respectively). Non ocular TEAEs occurring in ≥ 10% of subjects in either the VTE2Q4+PRN group or sham + VTE group were (respectively) nasopharyngitis (15.4% versus 25.0%) and hypertension (9.3% versus 10.3%). Non ocular TEAEs reported in ≥ 5% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were influenza (7.7% versus 2.9%) and back pain (6.7% versus 4.4%).

In COPERNICUS, the incidence of non ocular SAEs was higher in subjects in the sham + VTE group (19 [25.7%]) than in the VTE2Q4+PRN group (24 [21.1%]).The most commonly reported non ocular SAEs reported in ≥ 2 subjects in the VTE2Q4+PRN group (versus the sham + VTE PRN group) were: inguinal hernia (2 [1.8%] versus 0 [0%]); urinary tract infection (2 [1.8%] versus 0 [0%]); and coronary artery stenosis (2 [1.8%] versus 0 [0%]). Non ocular SAEs reported in ≥ 2 subjects in the sham + VTE PRN group (versus the VTE2Q4+PRN group): were pneumonia (2 [ 5.4%] versus 0 [0%]); pancreatitis (2 [2.7%] versus 0 [0%]); colon cancer (2 [2.7%] versus 0 [0%]); and renal failure acute (2 [2.7%] versus 1 [0.9%]). All other non ocular SAEs each occurred in no more than 1 subject in either treatment group.

In GALILEO, the incidence of non ocular SAEs from baseline to Week 76 was higher in subjects in the sham + VTE group (10/68 [14.7%]) than in the VTE2Q4+PRN group (12/104 [11.5%]). There were no non ocular SAEs reported in more than 1 subject in the VTE2Q4+PRN group and the only non ocular SAE reported in more than 1 subject in the sham + VTE PRN group was syncope (2 [2.9%]).

In COPERNICUS, the overall proportion of subjects who experienced at least 1 non ocular TEAE of interest from baseline to Week 100 was similar in the sham + VTE PRN and VTE2Q4 groups (50 [67.6%] versus 72 [63.2%], respectively). Hypertension was the most common (≥ 10% of all subjects) non ocular TEAE of interest and occurred in 22 (19.3%) subjects in the VTE2Q4+PRN group and 12 (16.2%) subjects in the sham + VTE PRN group. No other non ocular TEAEs of interest were reported in ≥ 10% of subjects in either treatment group. Hypertension was the only non ocular TEAEs of interest reported in ≥ 2% more subjects in the VTE2Q4+PRN group than in the sham + VTE PRN group.

In GALILEO, the overall proportion of subjects who experienced at least 1 non ocular TEAE from baseline to Week 76 was similar in the sham + VTE PRN group (8 [11.8%]) and the VTE2Q4+PRN group (13 [12.5%]). The only non ocular TEAE of interest occurring in ≥ 10% of subjects in either treatment group was hypertension (7 [10.3%], sham + VTE PRN versus 10 [9.6%], VTE2Q4+PRN). No non ocular TEAEs of interest were reported in ≥ 2% more subjects in the VTE2Q4+PRN group than in the sham + VTE PRN group.

In COPERNICUS, there were 4 deaths from the start of the study through Week 100 and all occurred in the sham + VTE PRN group (1 arrhythmia; 1 acute MI; 1 oesophageal adenocarcinoma stage IV; 1 pneumonia). In GALILEO, no deaths occurred through to Week 76.

In COPERNICUS and GALILEO, no clinically significant changes in laboratory tests (haematology, clinical chemistry, urinalysis), vital signs or electrocardiogram (ECG) findings (assessed in GALILEO only) occurred over the duration of the studies in subjects

in the VTE2Q4+PRN or sham + VTE PRN groups. There were no notable clinically significant changes in liver or renal function tests associated with VTE treatment in either study.

In COPERNICUS, the proportions of subjects with increases in IOP of 10, 21 or 35 mmHg from baseline through Week 100 were higher in the sham + VTE PRN group than in the VTE2Q4 group: (a) ≥ 10 mmHg from baseline to pre dose, 13.5% versus 7.0%; (b) absolute value of ≥ 21 mmHg pre dose, 31.1% versus 26.3%; and (c) absolute value ≥ 35 mmHg at any time, 6.8% versus 1.8%. In GALILEO, the proportions of subjects with increases in IOP of 10, 21 or 35 mmHg at least once from baseline through Week 76 were higher in the VTE2Q4+PRN group than in the sham + VTE PRN group: (a) ≥ 10 mmHg from baseline to pre dose, 9.6% versus 7.4%; (b) absolute value of ≥ 21 mmHg pre-dose, 19.2% versus 13.2%; and (c) absolute value ≥ 35 mmHg at any time, 4.8% versus 1.4%.

Immunogenicity assessment at Week 52 showed that treatment emergent Anti-drug antibodies (ADAs) in the VTE2Q4+PRN group occurred in 2.6% (3/114) of subjects in COPERNICUS and 2.9% (3/104) of subjects in GALILEO. None of subjects who tested positive for ADA tested positive for neutralising antibodies. The number of ADA positive subjects was too small to allow for meaningful conclusions to be drawn about the effects of ADA on efficacy and safety.

**Safety issues associated with switch from proactive monthly dosing to reactive PRN dosing**

The major safety issue relates to the increased incidence of macular oedema and other CRVO disease related TEAEs following switching from the initial proactive VTE2Q4 treatment regimen from Week 0 through to Week 24 to a VTE PRN regimen from Week 24 onwards. The increased incidence of CRVO disease related TEAEs (particularly marked for macular oedema and reduced visual acuity) following the switch suggests that the condition regresses when proactive treatment is discontinued and reactive treatment is instituted (see Table 8 below). However, interpretation of the data in the VTEP2Q4+PRN group during the reactive (PRN) period is complicated as macular oedema, reduced visual acuity and cystoid macular oedema all occurred less frequently in the sham and sham + VTE groups than in the VTE2Q4+PRN group. The safety data indicate that a proactive VTE2Q4 regimen can control CRVO disease-related TEAEs at least for the first 24 weeks of treatment and suggests that a VTE2Q4 regiment after the first 24 week might be superior to a VTE PRN in preventing recurrence of CRVO disease-related TEAEs.

**Table 8: Integrated Analysis – Common CRVO disease-related TEAEs in the proactive period (Week 0 Week 24) and the reactive PRN period (Week 24 to Week 52) in subjects completing 52 weeks.**

| | Week 0 to Week 24 (proactive treatment) | | | Week 24 to Week 52 (reactive treatment) | | |
|---|---|---|---|---|---|---|
| | Sham (G) n=68 | Sham (C) n=74 | VTE2Q4 (G+C) n=218 | Sham (G) n=57 | Sham + VTE PRN (C) n=60 | VTE2Q4+PRN (G+C) n=207 |
| Macular oedema | 11 (16.2%) | 1 (1.4%) | 3 (1.4%) | 6 (10.5%) | 0 (0%) | 44 (21.3%) |
| Visual acuity reduced | 7 (10.3%) | 3 (17.6%) | 9 (4.1%) | 1 (1.8%) | 3 (5.0%) | 27 (13.0%) |
| Cystoid macular oedema | 0 (0%) | 1 (1.4%) | 1 (0.5%) | 0 (%) | 2 (3.3%) | 12 (5.8%) |
| Retinal haemorrhage | 4 (5.9%) | 6 (8.1%) | 7 (3.2%) | 5 (8.8%) | 3 (5.0%) | 12 (5.8%) |

Not unexpectedly, injection related ocular TEAEs occurred more commonly in subjects in the 2 to 3 injections sub group than in the ≥ 4 injections sub group (see Table 9, below). Conjunctival haemorrhage, eye irritation and eye pain were all notably more common in subjects in the ≥ 4 injections sub group than in the ≥ 2 to 3 injections sub group. However, the sponsor stated that injection related AEs "*were not considered to be serious and would most likely subside after injection with no [additional] sequelae expected*".

**Table 9: Integrated Analysis – Common (≥ 3 subjects in any group) injection related AEs by dosing sub group from Week 24 to Week 52; subjects completing Week 52.**

| | ≤ 3 injections N=139 | 2-3 injections N=88 | ≥ 4 injections N=59 |
|---|---|---|---|
| Conjunctival hemorrhage | 5 (3.6) | 5 (5.7) | 7 (11.9) |
| Eye irritation | 2 (1.4) | 2 (2.3) | 5 (8.5) |
| Eye pain | 5 (3.6) | 3 (3.4) | 5 (8.5) |
| Injection site pain | 3 (2.2) | 2 (2.3) | 1 (1.7) |
| IOP increased | 3 (2.2) | 3 (3.4) | 3 (5.1) |
| Lacrimation increased | 3 (2.2) | 3 (3.4) | 2 (3.4) |
| Ocular hyperemia | 2 (1.4) | 2 (2.3) | 3 (5.1) |

The most commonly occurring CRVO disease-related TEAEs in the three injection groups are summarised below in Table 10. The most noteworthy differences between the 2 to 3 injections and ≥ 4 injections sub groups relate to the greater proportion of subjects with macular oedema in subjects in the 2 to 3 injections sub group compared with the ≥ 4 injections sub group and the greater proportion of patients with reduced visual acuity in the ≥ 4 injections sub group compared with the 2 to 3 injections sub group. There were no marked differences between the 2 to 3 injections and ≥ 4 injections sub groups for other common CRVO disease-related TEAEs. Serious CRVO disease-related TEAEs of the study eye (2 to 3 versus ≥ 4 sub groups) were macular oedema (3.4% versus 1.7%), cystoid macular oedema (1.1% versus 0%), and visual acuity reduced (1.1% versus 0%).

**Table 10: Integrated Analysis – Common CRVO disease-related TEAEs by dosing sub group from Week 24 to Week 52; subjects completing Week 52.**

| | ≤ 3 injections (n=139) | 2-3 injections (n=68) | ≥ 4 injections (n=59) |
|---|---|---|---|
| Macular oedema | 23.7% (n=33) | 34.1% (n=30) | 18.6% (n=11) |
| Visual acuity reduced | 10.1% (n=14) | 13.6% (n=12) | 20.3% (n=12) |
| Cystoid macular oedema | 5.0% (n=7) | 8.0% (n=7) | 8.5% (n=5) |
| Macular degeneration | 1.4% (n=2) | 2.3% (n=2) | 0% |
| Retinal haemorrhage | 5.8% (n=8) | 4.5% (n=4) | 6.8% (n=4) |
| Retinal pigment epitheliopathy | 2.2% (n=3) | 2.3% (n=2) | 0% |
| Retinal neovascularisation | 0.7% (n=1) | 1.1% (n=1) | 1.7% (n=1) |

TEAEs of interest occurred in a higher proportion of subjects in the ≥ 4 injections sub group (27/59 [45.8%]) compared with the 2 to 3 injections sub group (31.8% [28/88]). TEAEs of interest occurring in ≥ 2% of subjects in the ≥ 4 injections sub group and in ≥ 2% more subjects than in the 2 to 3 injections sub group were: visual acuity reduced (20.3% versus 13.6%); visual impairment (3.4% versus 1.1%); conjunctival haemorrhage (11.9% versus 5.7%); and eye pain (8.5% versus 3.3%).

## First round benefit-risk assessment

### First round assessment of benefits

The benefits of treatment for the proposed usage primarily relate to improvement in BCVA and reduction in CRT. In both COPERNICUS and GALILEO, the proportion of subjects gaining 15 or more letters in the ETDRS letter score at Week 24 (pre specified primary efficacy analysis adjusted for baseline region and BCVA) was clinically and statistically significantly greater in the VTE2Q4 group than in the sham group. In both COPERNICUS and GALILEO, the improvements in BCVA observed at Week 24 in the VTE2Q4 groups were largely maintained through to Week 52 following a switch to VTE PRN at Week 24.

In COPERNICUS, 56.1% (64/114) of subjects in the VTE2Q4 group gained 15 or more letters at Week 24 compared with 12.3% (9/73) of subjects in the sham group, with the adjusted difference between the two groups being 44.8% (95% CI: 33.0, 56.6), p<0.0001. In GALILEO, 60.2% (62/103) of subjects in the VTE2Q4 group gained 15 or more letters at Week 24 compared with 22.1% (15/68) in the sham group, with the adjusted difference between the two groups being 38.3% (95% CI: 24.4, 52.1), p<0.0001. In the primary efficacy analysis, in COPERNICUS discontinued subjects before Week 24 with < 5 injections were assessed as treatment failures (otherwise LOCF), while in GALILEO discontinued subjects before Week 24 were assessed as treatment failures.

In COPERNICUS, the results for all four secondary efficacy endpoints at Week 24 (analysed in a pre specified hierarchical manner to account for multiplicity) clinically and statistically significantly favoured VTE2Q4 compared with sham (that is, change from baseline in BCVA score at Week 24, change from baseline in CRT at Week 24, progression to any neovascularisation at Week 24, and change from baseline in the NEI VFQ-25 total score at Week 24). In GALILEO, there were five secondary efficacy endpoints and clinically and statistically significant differences in favour of VTE2Q4 compared with sham were seen for the first two endpoints tested using the pre specified hierarchical sequence (that is, change from baseline in BCVA score at Week 24 and change from baseline in CRT at Week 24). However, as there was no statistically significant difference between the two treatments for the third secondary efficacy endpoint in the testing sequence (that is, progression to any neovascularisation at Week 24) hypothesis testing was stopped. Therefore, for the sequential fourth and fifth secondary efficacy endpoints, the p values for the comparisons between the two treatment groups were nominal rather than confirmatory (that is, changes from baseline in the NEI VFQ-25 total score [fourth endpoint] and the EQ-5D total score [fifth endpoint] at Week 24).

Following switching to VTE PRN at Week 24, BCVA was largely maintained through to Week 52 in the VTE2Q4+PRN groups in both COPERNICUS and GALILEO. In COPERNICUS, the proportion of subjects in the VTE2Q4+PRN group who gained at least 15 letters from baseline at Weeks 24 and 52 were 56.1% and 55.3%, respectively. In GALILEO, the proportion of subjects in the VTE2Q4+PRN group who gained at least 15 letters from baseline at Weeks 24 and 52 were 60.2% and 58.3%, respectively. In COPERNICUS, the mean improvement from baseline in the BCVA in the VTE2Q4+PRN group at Weeks 24 and 52 was 17.3 and 16.2 letters, respectively (that is, a loss of approximately 1 letter between the two time-points). In GALILEO, the mean improvement from baseline in the BCVA in the VTE2Q4+PRN group at Weeks 24 and 52 was 18 and 16.9 letters, respectively (that is, a loss of approximately 1 letter between the two time-points). In both studies, subjects in the VTE2Q4 group experienced improvement in the BCVA letter score by the first post baseline measurement at Week 4, which continued over the course of treatment until about Week 16/Week 20 after which BCVA stabilised at a mean improvement of about 17 to 18 letters compared with baseline. In contrast, in subjects in the sham group in GALILEO there was only a minor improvement in BCVA letter score from baseline to Week 24 (gain of 3.3 letters), and in COPERNICUS there was no improvement in BCVA from baseline to Week 24 (loss of 4.0 letters).

Following switching to VTE PRN at Week 24, in the VTE2Q4+PRN groups the mean CRT increased from week 48 to Week 52 by approximately 44 µm in COPERNICUS (from 204.5 to 248.7 µm), and by approximately 25 µm in GALILEO (from 234.6 to 259.7 µm). These results suggest destabilisation of the disease following switching and are consistent with the increased risk of macular oedema in the reactive (PRN) dosing phase compared with the proactive (VTE2Q4) dosing phase.

In both studies, BCVA decreased and CRT increased from Week 52 in the VTE2Q4+PRN groups through to Week 100 in COPERNICUS and through to Week 76 in GALILEO. In both studies, the changes from Week 52 to study end in the VTE2Q4+PRN group was more marked than the changes from Week 24 to Week 52, which reflects the longer period between assessments in the 52 weeks onwards reactive PRN phase, 3 months in COPERNICUS and 2 months in GALILEO, compared with 4 weeks in the Week 0 to Week 24 proactive phase in both studies.

### First round assessment of risks

Eylea (VTE) administered by IVT injection (2 mg) was generally well tolerated and the safety profile of the drug for the treatment of CRVO is consistent with the known safety

profile for the treatment of wet AMD. The main risks associated with VTE in the treated eye related to ocular TEAEs, injection related TEAEs and increased incidence of CRVO disease related TEAEs following switching to a reactive treatment regimen (VTE 2 mg PRN) following the first 6 months of proactive treatment with VTE2Q4. VTE had no notable effects on ocular TEAEs in the fellow eye compared with sham or sham + VTE PRN. VTE had no significant clinical effects on non ocular TEAEs, including arterial thromboembolic events, compared with sham or sham + VTE PRN. There were no apparent clinically significant changes in laboratory parameters (haematology, clinical chemistry or urinalysis), vital signs or the ECG associated with VTE treatment.

***Risks in the first 24 weeks of treatment (integrated analysis)***

- the highest incidence of ocular TEAEs in the study eye occurred in subjects in the sham/COPERNICUS group (67.6%) followed by the sham/GALILEO (64.7%) and the combined VTE2Q4 (59.2%) groups. Commonly occurring ocular TEAEs in the study eye reported more frequently in subjects in the combined VTE2Q4 group than in subjects in both the sham/GALILEO and sham/COPERNICUS groups, respectively, were: eye pain (12.8% versus 4.4% versus 5.4%); macular fibrosis (4.1% versus 1.5% versus 1.4%); optic disc vascular disorder (6.0% versus 4.4% versus 1.4%); and vitreous floaters (5.0% versus 0% versus 2.7%). Macular oedema occurred notably more commonly in the sham/GALILEO (16.2%) group than in the sham/COPERNICUS and the combined VTE2Q4 groups (1.4% in each group).
- ocular injection related TEAEs in the study eye were reported in a higher proportion of subjects in the combined VTE2Q4 group than in the combined sham group (31.2% versus 22.5%). The most commonly reported ocular injection related TEAEs occurring in ≥ 2% more subjects in the combined VTE2Q4 group than in the combined sham group were eye pain (11.0% versus 3.5%) and IOP increased (5.5% versus 1.4%).
- serious ocular TEAEs in the study eye were reported in a higher proportion of subjects in the combined sham group than in the combined VTE2Q4 group (10.6% versus 2.8%). Serious ocular TEAEs in the study eye reported in 2 or more subjects occurred only in the sham group. One (1) subject (0.5%) in the VTE2Q4 group experienced an SAE of endophthalmitis. There were 2 deaths (1 acute myocardial infarction; 1 arrhythmia), both of which occurred in COPERNICUS in patients treated with sham and both of which were adjudicated as ATE/APTC events.
- ocular TEAEs of interest in the study eye were reported in a higher proportion of subjects in the combined sham group than in the combined VTE2Q4 group (35.9% versus 29.4%). Ocular TEAEs of interest (≥ 5% overall) in subjects in the combined VTE2Q4 group occurring more commonly than in the combined sham group were mild transient pain at the injection site (11.9% versus 4.9%), and transient increase in IOP (6.0% versus 1.4%).
- the proportion of subjects with at least one non ocular TEAE was higher in subjects in the sham/GALILEO group (54.4%) than in both the sham/COPERNICUS group (51.4%) and the combined VTE2Q4 group (48.6%). Overall, the most common non ocular TEAE was nasopharyngitis and this event was reported in a similar proportion of subjects in the combined sham and the combined VTE2Q4 groups (7.0% versus 6.0%, respectively). Hypertension occurred in a higher proportion of subjects in the combined VTE2Q4 group than in the combined sham group (6.4% versus 4.9%). The incidence of serious non ocular TEAEs was higher in subjects in the combined sham group than in the combined VTE24 group (7.7% versus 5.5%, respectively). In COPERNICUS, there were no ATE/APTC events in the VTE2Q4 group, while 2 subjects in the sham group experienced ATE/APTC events. In GALILEO, there were no ATE/APTC events in either the sham or VTE2Q4 treatment groups.

### *Risks from Week 0 through to Week 76 (GALILEO)*

- ocular TEAEs in the study eye were reported in a similar proportion of subjects in both treatment groups (75.0%, sham + VTE PRN versus 78.8%, VTE2Q4+PRN]). Ocular TEAEs occurring in ≥ 5% of subjects in the VTE2Q4+VTE group and in ≥ 2% more subjects than in the sham + VTE PRN group were: macular oedema (39.4% versus 25.0%); IOP increased (17.3% versus 5.9%); conjunctival haemorrhage (17.3% versus 7.4%); retinal haemorrhage (15.4% versus 11.8%); eye pain (14.4% versus 5.9%); ocular hyperaemia (8.7% versus 5.9%); vitreous detachment (6.7% versus 1.5%); vitreous floaters (6.7% versus 1.5%); iris neovascularisation (6.7% versus 0%); retinal vein occlusion (6.7% versus 0%); cystoid macular oedema (5.8% versus 1.5%); and injection site pain (5.8% versus 2.9%).
- injection related TEAEs in the study eye were reported in a marginally higher proportion of subjects in the VTE2Q4+PRN group than in the sham + VTE PRN group (42.3% versus 39.7%). Injection related TEAEs in the study eye occurring in ≥ 2% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: conjunctival haemorrhage (17.3% versus 7.4%); eye pain (13.5% versus 5.9%); IOP increased (12.5% versus 4.4%); foreign body sensation in eye (6.7% versus 4.4%); vitreous floaters (3.8% versus 1.5%); and ocular hypertension (2.9% versus 0%). All other injection related TEAEs occurred in a similar proportion of subjects in both treatment groups.
- ocular TEAEs of interest in the study eye were reported in a similar proportion of subjects in the VTE2Q4+PRN and sham + VTE PRN groups (43.3% versus 42.6%, respectively). Ocular TEAEs of pre specified interest in the study eye reported in ≥ 2% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: conjunctival haemorrhage (16.3% versus 4.4%); eye pain (13.5% versus 5.9%); IOP increased (12.5% versus 4.4%); visual impairment (4.8% versus 0%); vitreous floaters (3.8% versus 1.5%); and ocular hypertension (2.9% versus 0%).
- ocular SAEs in the study eye were reported in a marginally higher proportion of subjects in the VTE2Q4+PRN group than in the sham + VTE PRN group (10.6% versus 8.8%). The only ocular SAEs occurring in at least 2 subjects in the VTE2Q4+PRN group (vs sham + VTE PRN) were macular oedema (4 [3.8%] versus 2 [2.9%]), and visual acuity reduced (2 [1.9%] versus 1 [1.5%].
- non ocular TEAEs occurred in a higher proportion of subjects in the sham + VTE PRN group than in the VTE2Q4+PRN group (73.5% versus 68.3%). Non ocular TEAEs reported in ≥ 5% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were influenza (7.7% versus 2.9%) and back pain (6.7% versus 4.4%). The proportion of non ocular SAEs was higher in subjects in the sham + VTE group than in the VTE2Q4+PRN group (14.7% versus 11.5%). There were no non ocular SAEs reported in more than 1 subject in the VTE2Q4+PRN group. No subjects experienced ATE/APTC events. No deaths occurred.
- non ocular TEAEs of pre-specified interest were reported in similar proportion of subjects in the sham + VTE PRN and VTE2Q4+PRN groups (11.8% versus 12.5%, respectively). The only non ocular TEAE of interest occurring in ≥ 10% of subjects in either treatment group was hypertension, and this event was reported in a similar proportion of subjects in the sham + VTE PRN and VTE2Q4+PRN groups (10.3% versus 9.6%). No non ocular TEAEs of interest were reported in ≥ 2% more subjects in the VTE2Q4+PRN group than in the sham + VTE PRN group.

- immunogenicity was assessed at Week 52 and showed that 3/104 (2.9%) subjects in the VTE2Q4+PRN group were treatment emergent ADA positive but were negative for neutralising antibodies.

***Risks in Week 0 through to Week 100 (COPERNICUS)***

- ocular TEAEs in the study eye were reported in a similar proportion of subjects in the sham + VTE PRN and VTE2Q4+PRN groups (85.1% versus 87.7%, respectively). Ocular TEAEs occurring in ≥ 5% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: macular oedema (18.4% versus 4.1%); eye pain (18.4% versus 9.5%); retinal vascular disorder (12.3% versus 9.5%); cystoid macular oedema (13.2% versus 6.8%); optic disc vascular disorder (12.3% versus 8.1%); macular fibrosis (10.5% versus 8.1%); retinal exudates (11.4% versus 6.8%); eye irritation (7.9% versus 5.4%); vitreous floaters (7.9% versus 5.4%); cataract (7.0% versus 4.1%); maculopathy (6.1% versus 2.7%); and ocular hyperaemia (5.3% versus 0%).
- injection related TEAEs in the study eye were reported in a higher proportion of subjects in the VTE2Q4+PRN group than in the sham + VTE PRN group (39.5% versus 28.4%). Injection-related TEAEs in the study eye occurring in ≥ 2% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: eye pain (13.2% versus 5.4%); vitreous floaters (4.4% versus 1.4%); ocular hyperaemia (4.4% versus 0%); IOP increased (2.6% versus 0%); punctate keratitis (2.6% versus 0%); and vitreous detachment (2.6% versus 0%). All other injection related TEAEs occurred in a similar proportion of subjects in both treatment groups.
- ocular TEAEs of pre specified interest in the study eye were reported in a similar proportion of subjects in the sham + VTE PRN and VTE2Q4+PRN groups (52.7% versus 50.9%, respectively). Ocular TEAEs of interest in the study eye occurring in ≥ 2% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: eye pain (13.2% versus 5.4%); vitreous floaters (4.4% versus 1.4%); and IOP increased (2.6% versus 0%). The proportion of subjects who experienced at least one ocular SAE of interest was low in both treatment groups (1.4%, sham + VTE PRN versus 1.8%, VTE2Q4+PRN). In the sham + VTE PRN group, the SAE was visual acuity reduced, and in the VTE2Q4+PRN group the 2 SAEs were visual acuity reduced and endophthalmitis.
- ocular SAEs in the study eye were reported about twice as frequently in subjects in the sham + VTE PRN group than in the VTE2Q4+PRN group (16.2% versus 8.8%). The most commonly reported ocular SAE in the study eye in the VTE2Q4+PRN group was cataract (3.5% VTE2Q4+PRN versus 1.4% sham + VTE PRN). The only other ocular SAE in the study eye reported in ≥ 1 % of subjects in the VTE2Q4+PRN group and more commonly than in the sham + VTE PRN group was cystoid macular oedema (1.8% versus 0%).
- non ocular TEAEs were reported in a similar proportion of subjects in the sham + VTE PRN and VTR2Q4+PRN groups (81.1% versus 77.2%, respectively). Non ocular TEAEs reported in ≥ 5% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in the sham + VTE PRN group were: hypertension (19.3% versus 16.2%); nasopharyngitis (8.8% versus 6.8%); upper respiratory tract infection (8.8% versus 5.4%); influenza (7.9% versus 5.4%); bronchitis (6.1% versus 4.1%); sinusitis (6.1% versus 4.1%); urinary tract infection (6.1% versus 4.1%); and anaemia (5.3% versus 2.7%).
- non ocular SAEs were reported in a marginally higher proportion of subjects in the sham + VTE group than in the VTE2Q4+PRN group (25.7% versus 21.1%). Non ocular SAEs reported in ≥ 2 subjects in the VTE2Q4+PRN group (versus the sham + VTE PRN

group) were: inguinal hernia (2 [1.8%] versus 0 [0%]); urinary tract infection (2 [1.8%] versus 0 [0%]); and coronary artery stenosis (2 [1.8%] versus 0 [0%]). There were 4 deaths reported over the 100 weeks of the study and all occurred in the sham + VTE PRN group (1 arrhythmia; 1 acute MI; 1 oesophageal adenocarcinoma stage IV; 1 pneumonia).

- non ocular TEAEs of pre-specified interest were reported in a similar proportion of subjects in the sham + VTE PRN and VTE2Q4+PRN groups (67.6% versus 63.2%, respectively). Hypertension was the only reported non ocular TEAE of interest reported in ≥ 10% of subjects in both treatment groups and was reported in a higher proportion of subjects in the VTE2Q4+PRN group than in the sham + VTE PRN group (19.3% versus 16.2%). Hypertension was the only non ocular TEAE of interest reported in ≥ 2% more subjects in the VTE2Q4 group than in the sham + VTE PRN group.
- immunogenicity was assessed at Week 52 and showed that 3/114 (2.6%) subjects in the VTE2Q4+PRN group were treatment emergent ADA positive, but were negative for neutralising antibodies.

***Risk of CRVO disease regression following switch from proactive to reactive regimen***

In subjects switching from VTE2Q4 to VTE PRN after the first 6 months of proactive treatment there was an increased incidence of CRVO disease related TEAEs (particularly marked for macular oedema and reduced visual acuity). This observation suggests that CRVO regresses when proactive treatment is discontinued and reactive treatment is instituted. Consequently, a continuous proactive treatment regimen might mitigate the risk of disease regression associated with switching from a proactive regimen (VTE2Q4) to a reactive VTE PRN treatment regimen after the first 6 months of treatment.

There are no confirmatory data indicating that a proactive regimen from six months onwards will prevent an increase in CRVO disease related TEAEs (in particular macular oedema and reductions in visual acuity). However, there are data from which it can be inferred that a VTE2Q4 regimen might be effective in reducing CRVO disease related TEAEs following a switch from proactive to reactive dosing. The data for a proactive VTE2Q4 regimen from six months onwards is considered to be stronger than for the sponsor's proposed proactive VTE2Q8 regimen.

**First round assessment of benefit-risk balance**

The benefit-risk balance of Eylea, given the proposed usage, was considered to be favourable.

## First round recommendation regarding authorisation

It was recommended that Eylea be approved for the *treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).* The inclusion criteria for both COPERNICUS and GALILEO included subjects with visual impairment in addition to macular oedema secondary to CRVO and the primary efficacy outcome in both studies was improvement in BCVA following treatment. Therefore, it is considered that treatment should only be initiated in subjects with visual impairment due to macular oedema secondary to CRVO. There are no data on whether treatment with Eylea in subjects with macular oedema secondary to CRVO but without visual impairment will prevent the development of visual impairment.

## Clinical questions

### Pharmacokinetics

No questions.

### Pharmacodynamics

No questions.

### Efficacy

a. In GALILEO, the Week 76 data indicate that from baseline to Week 76, 39 (36.8%) subjects in the VTE2Q4+PRN group had major protocol deviations characterised by treatment deviations compared with 11 (15.5%) subjects in the sham + VTE PRN group. What was the nature of the treatment deviations reported in each treatment group, and what was the reason for the notable difference in treatment deviations between the two treatment groups?

b. The proportion of subjects with major protocol deviations over the course of the study was notably higher in GALILEO than in COPERNICUS (40.1% [71/17] through to Week 76 versus 4.8% [9/189] through to Week 100, respectively). Please comment on the reasons for the difference between the two studies.

### Safety

c. In the integrated analysis, macular oedema was reported more commonly in subjects in the Week 24 to 52 period than in the Week 0 to 24 period (21.3% versus 1.4%, respectively), as was reduced visual acuity (13.0% versus 4.1%, respectively). The differences may reflect the switch from proactive VTE2Q4 dosing from Week 0 to Week 24 to reactive VTE PRN dosing from Week 24 to 52 and raises the possibility that rebound macular oedema occurs when VTE dosing is changed from proactive to reactive. However, the sponsor appears to consider that the observed results do not reflect a rebound effect. Please comment on the possibility that the higher incidence of macular oedema in Week 24 to 52 compared with Week 0 to 24 does reflect a rebound effect due to the switch from proactive to reactive dosing.

d. In the sponsor's Summary of Clinical Safety (Table 22 [16]; Week 24 to 52) non ocular TEAEs are stated to be sourced from Module 5.3.5.3 GIA_VEGF Trap-Eye_CRVO_1y data Table 14.3.1.2/6. However, the total number of subjects in each of the groups in the source table differs from the corresponding numbers in Table 22 (that is, sham 57, not 68; sham + VTE 60, not 64; VTE2Q4 207, not 218; and Total 324 not 360). Furthermore, the number and percentages given in Table 22 relate to the total number of subjects in each group in the source table and not in each group in Table 22, and the percentage of subjects given for the number of subjects with at least one non ocular TEAE in the sham group (59.9%) appears to be incorrect (should be 50.9% [29/57]). It appears that the total numbers in Table 22 reflect the SAF population rather than the population who completed Week 24 and were treated through to Week 52. Please comment on these apparent discrepancies.

[16] Not in this AusPAR.

e. In the COPERNICUS CSR (Week 100), it is stated ("*Prespecified ocular adverse events of special interest*") that "F*rom baseline to Week 100, the overall incidence of subjects who experienced at least 1 ocular TEAE of interest in the study eye was similar in the sham + VTE PRN group (67.6%) and the VEGF Trap-Eye 2Q4+PRN group (63.2%)*". However, the summary in Table 56[17] suggests that these percentages refer to all TEAEs of interest and that the relevant proportions for ocular TEAEs of interest are 52.7% and 50.9%. Similarly, on page 128 it is stated that "[*f]rom weeks 24 to 100, the number of subjects with at least 1 ocular TEAE of interest in the study eye was similar between the Sham+PRN and VEGF Trap-Eye 2Q4+PRN groups (51.7% and 48.2%, respectively)*". However, the summary in Table 57[18] suggests that these percentages refer to all TEAEs of interest, and that the relevant proportions for ocular TEAEs of interest are 33.3% and 38.2%. Please comment on these apparent discrepancies.

f. In the COPERNICUS CSR (Week 100), it is stated ("P*respecified non ocular adverse events of special interest*") that "*From baseline to Week 100, the overall incidence of subjects who experienced at least 1 non ocular TEAE of interest in the study eye was similar in the Sham+PRN group (67.6%) and the VEGF Trap-Eye 2Q4+PRN group (63.2%)*". However, the summary in Table 59[19] suggests that these percentages refer to all TEAEs of interest and that the relevant proportions for non ocular TEAEs of interest are 31.1% and 25.4%, respectively. Similarly, on page 128 it is stated that "*From weeks 24 to 100, the number of subjects with at least 1 ocular TEAE of interest in the study eye was similar between the Sham+PRN and VEGF Trap-Eye 2Q4+PRN groups (51.7% and 48.2%, respectively)*". However, the summary in Table 60[20] indicates that these percentages refer to all TEAEs of interest and that the relevant proportions for ocular TEAEs of interest are 28.3% and 16.4%, respectively. Please comment on these apparent discrepancies.

**Dosing regimen**

g. The recommended Eylea dose in the USA for the treatment of macular oedema following central retinal vein occlusion (CRVO) is 2 mg (0.05 mL) administered every 4 weeks (monthly). However, in Australian the sponsor proposes that treatment with Eylea for the same indication be initiated with one injection per month (2 mg, 5 µL) for the first six months, followed by one injection (2 mg, 5 µL) every two months. Please comment on the reason for this difference.

There are no confirmatory data indicating that a proactive regimen from six months onwards will prevent an increased in CRVO disease related TEAEs (in particular macular oedema and reduction in visual acuity). However, there are data from which it can be inferred that a VTE2Q4 regimen might be effective in reducing CRVO disease related TEAEs following a switch from proactive to reactive dosing. The data for a proactive VTE2Q4 regimen from six months onwards is considered to be stronger than for the sponsor's proposed proactive VTE2Q8 regimen. Please comment on why the sponsor proposes a VTE2Q8 regimen rather than a VTE2Q4 regimen from six months onwards.

[17] Not in this AusPAR.
[18] Not in this AusPAR.
[19] Not in this AusPAR.
[20] Not in this AusPAR.

## Second round evaluation of clinical data submitted in response to questions

This is the second round clinical evaluation report (CER2) of the sponsor's submission to extend the indication to include *macular oedema following central retinal vein occlusion (CRVO).*

This section of the report reviews the sponsor's response of 26 April 2013 addressing the clinical questions raised following the first round clinical evaluation (CER1) of the submission.

The major clinical issue raised in the sponsor's response relates to the sponsor's revised "*posology recommendation for the proposed CRVO indication*" The revised dosage recommendation is:

> *"Eylea treatment is performed with one intravitreal injection per month for three consecutive doses.*
>
> *The treatment interval* may then be extended beyond one month based on visual and anatomic outcomes."

The sponsor indicates that in proposing the revised posology it has considered the clinical evaluator's comments relating to dosage provided to the TGA and the comments from the European Medicines Agency (EMA) concerning the same application. The sponsor states that the "*revised posology recommendation proposed in the present response submission to the TGA is the same as that currently being proposed in Europe for consideration*".

The sponsor's response did not include amended Product Information (PI) and Consumer Medicine Information (CMI) documents. The sponsor plans to submit an amended PI following second round clinical evaluation comments on its revised "*"treat-and-extend" posology*".

The first (CER1) and second (CER2) round clinical evaluations have been undertaken by the same clinical evaluator. The two reports are complementary and should be reviewed together when considering the sponsor's submission to extend the indication to include macular oedema following CRVO.

In some cases the sponsor's responses are summarised to include only the key data submitted.

## Evaluation of the sponsor's response

### *Efficacy*

*Question a*

**Sponsor's response**

The notable difference in treatment deviations between the two groups was due to the fact that in the GALILEO study, every patient who was not treated with VTE when indicated by the predefined retreatment criteria in the PRN phase was counted as a major protocol deviation.

This reason is further supported by the observed evolution of the differences over the study duration, where a more clear connection becomes visible between the number of major protocol deviations characterised by treatment deviations and the VTE treatment given under a PRN regimen.

- As seen in the Week 0 to 24 data (during the fixed regimen), almost no major treatment deviations are seen in both groups.
- Comparison of the Week 0 to 24 data and the Week 0 to 52 data shows an apparent increase in the number of major treatment deviations in the VTE2Q4 group as the study enters into its PRN phase. The number of subjects with major treatment deviations in the VTE2Q4 group was increased to 29 (0 to 52 week); whereas the number of subjects with major treatment deviations in the Sham group remains largely unchanged.
- Further comparison with the Week 0 to 76 data shows that an increase in major "*treatment deviation*" is also observed in the Sham group that has been switched to VTE PRN treatment at Week 52. The number of subjects with major treatment

deviations in the Sham + VTE PRN group increased from 2 (Week 0-52) to 11 (Week 0 to 72). The increase observed in the VTE2Q4+PRN group was of a very similar magnitude: 29 (Week 0 to 52) and 39 (Week 0 to 72).

**Evaluator's comment**

The sponsor's explanation for the discrepancy is satisfactory. The data indicate that the increased percentage of treatment deviations from Week 0 to Week 76 in subjects in the VTE2Q4+PRN group compared with the sham+PRN VTE group was related to the increased chance of being treated with VTE PRN in the former compared with the latter group.

In the Week 0 to 24 data (during the fixed dose regimen) the percentage of subjects with major protocol deviations was similar in both the sham and VTE2Q4 groups (14.1%, 10/71 and 14.2%, 15/106; respectively). Furthermore, treatment deviations resulting in major protocol deviations were reported in 0 subjects in the sham group and 1 subject in the VTE2Q4 group.

In the sham group, subjects received sham injections every 4 weeks from Week 0 to Week 48, while in the VTE2Q4+PRN group subjects received VTE 2 mg every 4 weeks from Week 0 to Week 20 and were then eligible for PRN treatment with VTE from Week 24 to week 48. Therefore, in the Week 24 to 52 period patients in the sham group had a lower risk of being treatment deviators because they were not exposed to PRN VTE. This would account for the smaller number of treatment deviations in the Week 0 to 52 period in the sham group compared with the VTE2Q4+PRN group (2 [2.8%] versus 29 [27.4%]).

However, from Week 52 to Week 76 subjects in both the sham and VTE2Q4+PRN groups were eligible to receive VTE 2 mg or sham according to re treatment criteria. The Week 0 to 76 data indicate that 11 (15.5%) treatment deviations occurred in the sham + VTE PRN group compared with 39 (36.8%) in the VTE+PRN group. Comparison of the Week 0 to 52 and Week 0 to 76 data indicate that in the Week 52 to 76 period (when subjects in both treatment groups could have been treated with VTE PRN), treatment deviations were reported in 9 (12.7%) subjects in the sham + VTE PRN group and 10 (9.4%) subjects in the VTE2Q4+PRN group.

*Question b*

**Sponsor's response**

The notable difference between the two studies is due to different handling of deviation from the retreatment criteria in both studies.

In case a subject had received treatment in the PRN period that was not in accordance with what he/she was supposed to receive according to the predefined retreatment criteria, this was counted as a protocol deviation in GALILEO but not in COPERNICUS.

An in depth integrated analysis was conducted to evaluate the match between meeting the protocol specified retreatment criteria and actually receiving an active PRN injection over the full study duration of the GALILEO and COPERNICUS.

From Week 24 to Week 76/100 in the total population of 207 subjects, 3 (1.4%) subjects discontinued study medication during the fixed dose and could not be a part of the PRN dosing regimen; 132 (63.8%) showed a perfect match between meeting at least one retreatment criterion and receiving an active injection; 69 (33.3%) subjects had at least one mismatch, met at least one retreatment criterion but did not receive an active injection; and 10 (4.8%) subjects with at least one mismatch, did not meet the retreatment criterion but received an active injection. These data demonstrates that in about one third of the subjects, the treatment was not administered when it should have been based on the retreatment criteria.

**Evaluator's comment**

The sponsor's response was considered to be acceptable. The data provided in the fourth paragraph of the sponsor's response refers to the pooled VTE2Q4+PRN group (see Table 11, below). Overall, the data are similar for the two treatment groups and show that the proportion of subject with at least one mismatch between PRN injection and re treatment criteria was similar in the sham + VTE PRN and VTE2Q4+PRN treatment groups (33.3% [33/99] and 34.8% [72/207], respectively).

**Table 11: Proportion of subjects with matches/mismatches between injections and retreatment criteria from end of fixed dose (that is Week 24) to Week 76/100 on scheduled and unscheduled visits (subjects completing fixed dose).**

| | PRN (following sham, after 1st PRN) N=99 (100%) | VTE 2Q4 + PRN N=207 (100%) |
|---|---|---|
| Number of subjects who discontinued study medication during fixed dose | 0 | 3 ( 1.4%) |
| Number of subjects with total match between active injections and retreatment criteria [a] | 66 ( 66.7%) | 132 ( 63.8%) |
| Number of subjects with at least one mismatch between injections and retreatment criteria | 33 ( 33.3%) | 72 ( 34.8%) |
| At least one retreatment criterion fulfilled, but no active injection | 21 ( 21.2%) | 69 ( 33.3%) |
| No retreatment criterion fulfilled, but active injection | 13 ( 13.1%) | 10 ( 4.8%) |

Note: VTE 2Q4+PRN: VEGF Trap-Eye (VTE) administered at 2 mg every 4 weeks from day 1 to week 20 followed by administration as needed (PRN).
Note: PRN (following sham, after 1st PRN): includes all subjects receiving at least one active PRN injection and considers time period from 1st active PRN injection onwards.
Note: For the purpose of this table fixed dose period (up to week 24) includes Galileo sham period up to week 52.
Injections at unscheduled visits are counted.
Note: Injections are excluded when no retreatment criteria are available.
[a] Total match: For all visits active injection was given if any retreatment criterion was fulfilled and no active injection was given if no retreatment criterion was fulfilled.

## Safety

*Question c*

**Sponsor's response**

As stated in the sponsor's Summary of Clinical Safety, the changes in the VTE2Q4 group at Week 52 from the incidence noted at Week 24, especially for macular oedema (1.4% to 21.3%, respectively) and visual acuity reduced (4.1% to 13.0%, respectively) reflect the change from fixed monthly dosing to PRN dosing, the latter of which allowed for dosing only upon the observation of disease recurrence. Thus, it is not unexpected that disease related events would increase when treatment is reduced to the point of disease recurrence.

As noted by the evaluator, macular oedema and reduced visual acuity was reported as a TEAE in 44 (21.3%) patients and 27 (13%) patients, respectively, in Week 24 to 52 according to the integrated analysis submitted with the original Eylea submission. In depth analysis of all these cases of TEAE of macular edema and visual acuity revealed that in the treated patients, these events tended to occur after a longer period where no active injection was given and resolved quickly after administration of a VTE treatment.

The sponsor therefore does not consider the higher incidence of macular oedema in Week 24 to 52 compared with Week 0 to 24 in the integrated analysis reflects a rebound effect due to the switch from proactive to reactive dosing.

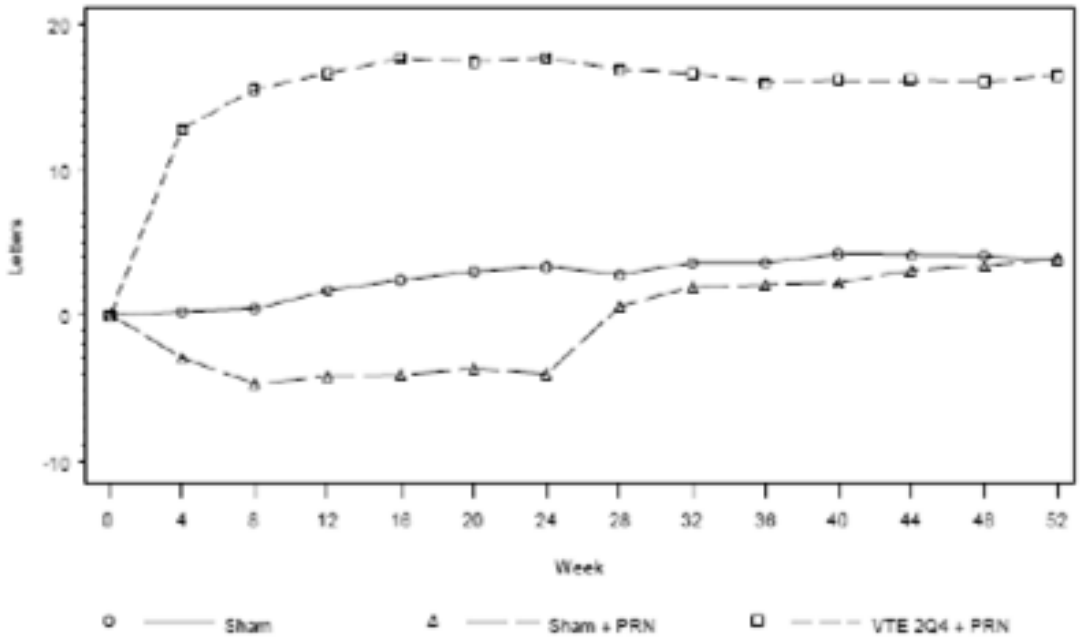
Furthermore, results from the integrated efficacy analysis demonstrates that majority of the subjects were able to maintain the improvements in vision and morphology achieved with proactive dosing of VTE2Q4 despite switching to a less frequent dosing in the PRN phase. There was little difference in the proportions of subjects who gained at least 15 letters in Week 0 to 24 (56.1% with proactive fixed VTE2Q4) compared to Week 24 to 52 (55.3% following a switch to reactive dosing based on the study retreatment criteria).

Similarly, significant improvement in BCVA was maintained in the VTE2Q4 group through to Week 52. Although there was a loss of approximately 1 letter in BVCA from Week 24 to 52, the increase in ETDRS letter score by 16.2 from baseline observed at the end of Week 52 remains statistically significant despite switching from a fixed VTE2Q4 dosing regimen

to a reactive dosing. The magnitude of a change in ETDRS letter score by 16.2 is considered clinically relevant. See Figure 1 below.

**Figure 1: Change in BCVA Letter Score from Baseline through Week 52**

**Circle=sham; triangle=sham+PRN and Square=VTE2Q4+PRN**




Note: Last observation carried forward (LOCF).
The missing values were replaced by the last observed post baseline values prior to the missing value

These efficacy findings further support the conclusion that there is no rebound effect when the dosing frequency of VTE is reduced to a reactive regimen in subjects who have reached stable disease.

**Evaluator's comment**

The sponsor's response was considered to be satisfactory.

*Question d*

**Sponsor's response**

The apparent discrepancies were due to an error in Table 22 in the sponsor's Summary of Clinical Safety. The figures presented in the source data from Module 5.3.5.3 GIA_VEGF Trap- Eye_CRVO_1y data Table 14.3.1.2/6 are correct.

Meanwhile, the sponsor has also become aware of a small discrepancy between Table 23 in the sponsor's Summary of Clinical Safety and the source data from Module 5.3.5.3 Integrated Efficacy and Safety Analysis (1 year data) Table 14.3.1.4/16.

The corrected Table 22 and Table 23 were provided to the TGA with matching source data.

**Evaluator's comment**

The sponsor's response was considered to be satisfactory. The amended safety data provided above in Tables 22 and 23 do not affect the assessment of safety in CER1.

### *Dosing regimen*

*Question e*

**Sponsor's response**

The US submission of Eylea in 2012 for the treatment of macular oedema following central retinal vein occlusion (CRVO) was based only on the 24 weeks data from both the GALILEO and COPERNICUS studies in which a fixed posology of VTE2Q4 dosing was evaluated. Results of the COPERNICUS and GALILEO studies beyond 24 weeks (which assessed the reactive posology of VTE PRN dosing) have not yet been reviewed by the FDA.

**Evaluator's comment**

The sponsor's response was considered to be satisfactory.

*Question f*

**Sponsor's response**

The sponsor has considered the evaluator's concerns about the proposed posology of a VTE2Q8 regimen from six months onwards and has taken the evaluator's comments into consideration to re-consider the appropriate dosing posology for CRVO taking into account all data from the entire study period, that is, the Week 76/100 data from the GALILEO and COPERNICUS studies, respectively, which were provided in our submission.

Of note from the Week 76/100 data from the GALILEO and COPERNICUS studies are that the treatment interval has been extended successfully in the PRN phase of the studies, resulting in a mean number of injections of 6.0 ± 3.4 active injections over the course of 100 weeks (median = 6.0; range of 0 to 15; Study VGFT-OD-0819, Week 100 CSR 14.1.4/4d) in COPERNICUS and of 3.7 ± 2.6 active injections over the course of 76 weeks (median = 4.0; range of 0 to 9; Study 14130 Week 76 CSR 14.1.4/20) in GALILEO.

The posology justification analysis that was provided in the submission dossier was based on the data as of Week 52 from the two pivotal studies.

To further address the question raised by the evaluator, additional analysis was conducted to also include the long-term data from Week 52 to the end of the GALILEO and COPERNICUS studies to further refine the posology recommendation to optimise the response to treatment with regards to vision whilst minimising over-treatment.

Based on the results of this analysis, the sponsor proposed a "treat-and-extend" dosing schedule to allow for a flexible dosing interval after the initial monthly doses instead of a switch from a fixed monthly to a fixed every two months dosing schedule. In such setting, the treating physician would need to determine based on visual and anatomic outcomes whether it is appropriate to extend the interval in order to avoid under or over treatment.

This 'treat-and-extend' dosing schedule therefore enables the treatment interval be adjusted individually based on the individual treatment response. Compared to the classical "PRN" treatment, where monitoring visits are scheduled on a fixed basis, a "treat-and-extend" schedule allows a more precise adjustment of the treatment interval in smaller increments and thereby aims treating towards optimised efficacy outcomes. In those patients, where the disease state allows, treatment is faded out and may ultimately be stopped.

### *GALILEO and COPERNICUS Integrated analysis – early treatment phase – to determine the optimal timeframe to extend the treatment interval*

In the context of the proposed "treat-and-extend" regimen, re analyses of the early treatment phase were conducted to determine the optimal timeframe to extend the treatment interval after being initially treated at a fixed monthly interval.

In both the GALILEO and COPERNICUS studies, the progression of the improvement in visual acuity over time showed a very steep initial rise, with most of the improvement becoming evident after the first 3 injections. This can be seen on the evaluation presenting 3 line gainer (Figure 2) as well as on the time course of mean changes in BCVA (Figure 3).

**Figure 2: Percent patients who gained ≥ 15 letters**

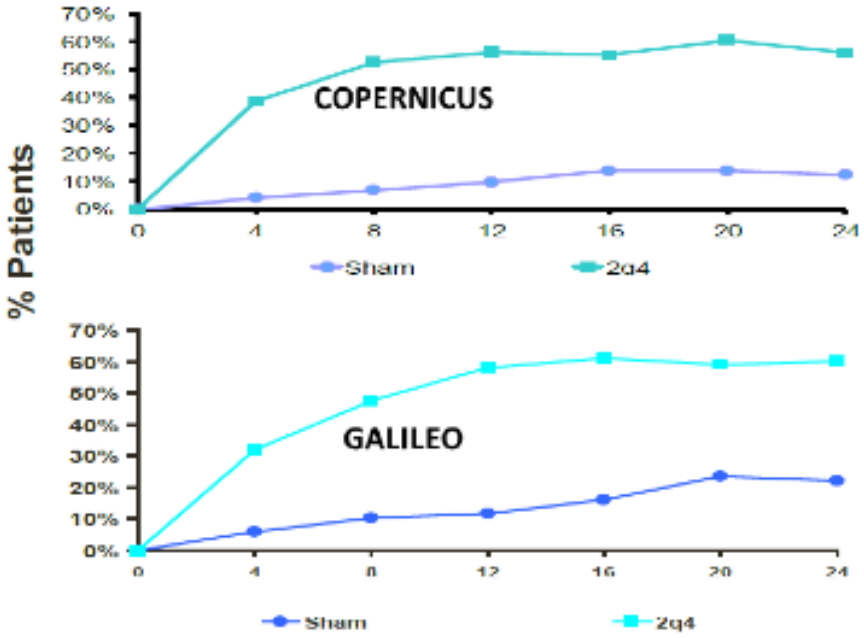
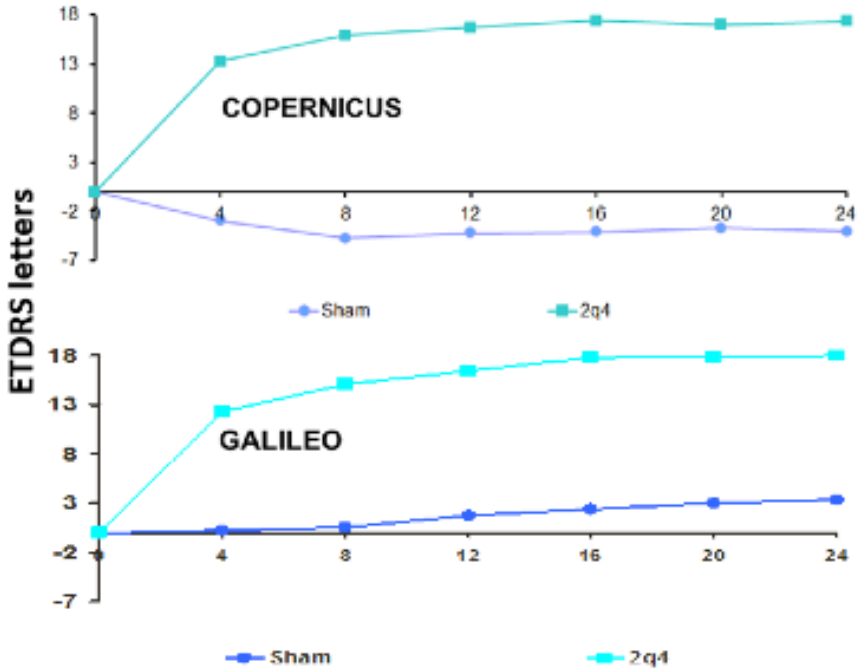



**Figure 3: Mean change in visual acuity**




***Summary findings for the optimal duration for initial VTE2Q4 treatment***

Due to the fast onset of the treatment effect, it appears appropriate to recommend that physicians may consider extension of the treatment interval after the third injection onwards.

***GALILEO and COPERNICUS Integrated analysis – Week 24 to Week 52 and Week 24 to Week 76/100 – to determine the change in BVCA achieved with a proactive fixed (Q4) dosing regimen compared to a reactive PRN dosing regimen***

To assess the BCVA behaviour once subjects were switched from a proactive treatment regimen to a reactive treatment regimen in which dosing was based on pre defined retreatment criteria, the subjects were divided into categories of "vision stability" as demonstrated at the last three visits in the fixed dosing phase (that is, Week 16, Week 20 and Week 24). Note that the first 3 months of the fixed dosing phase were not included in this comparison because the very steep rise in BCVA that is observed at the start of anti-VEGF therapy may have biased the comparison. The following categories of "vision stability" were defined (same as that used in the posology justification analyses originally submitted in the submission dossier):

**Excellent:** subject demonstrated a stable gain of 15 or more letters (that is, a gain of 15 or more letters over baseline) at the three assessed visits

**Good:** subject demonstrated a stable gain of 10 or more letters with all visits not showing a 15 letter or more gain (that is, a gain of 10 or more letters over baseline at the three assessed visits and the criteria for "excellent" were not met)

**Modest:** subject demonstrated a stable gain of 5 or more letters with all visits not showing a 10 letter or more gain (that is, a gain of 5 or more letters over baseline at the three assessed visits and the criteria for "excellent" and "good" were not met)

**Poor:** subject demonstrated a stable gain of 0 or more letters with all visits not showing a 5 letter or more gain (that is, a gain of 0 or more letters over baseline at the three assessed visits and the criteria for "excellent", "good", and "modest" were not met)

**No stable gain:** subject had at least one visit (in the three assessed visits) with a gain of fewer than 0 letters

**Missing:** Subject had at least one visit (in the three assessed visits) with missing data and no visit with a gain of fewer than 0 letters.

An investigation was undertaken to compare the slopes of regression lines derived from regression analyses within individual subjects and examined the slope of the change in BCVA (that is, BCVA could continue to improve [positive slope] or decline [negative slope]) at the end of the fixed dosing phase (Weeks 16 to 24) as compared to the slope of the change in BCVA through the full PRN phase of the studies for the five categories of vision stability (as well the missing and total subjects).

*As seen in Table 12 [NB: fixed dosing phase stability category Week 16 to Week 24 BCVA behaviour versus reactive PRN dosing phase Week 24 to Week 52 BCVA behaviour]*, about 32% (41 of 129 [88+41] subjects) of the subjects who demonstrated a positive slope in the fixed dosing phase experienced a decline in BCVA during the PRN dosing phase while receiving a median of 3 active injections. Conversely, about 68% of subjects who demonstrated a positive slope in the fixed dosing phase experienced an improvement (or no change) in BCVA during the PRN dosing phase, while receiving a median of 2 active injections.

**Table 12: Integrated analysis. BCVA behaviour in the fixed dosing phase versus the reactive dosing phase by stability categories achieved with fixed dosing (subjects completing Week 24)**

| | Each cell presents:<br>**Number** of subjects<br>**Median (Q1 – Q3)** number of injections in the PRN phase | | |
|---|---|---|---|
| **Fixed-dosing phase stability category[a]**<br>**BCVA behavior** | **Reactive PRN-dosing phase[b] BCVA behavior** | | |
| | **Improvement** | **Decline** | **Missing**<br>N (%) |
| **Excellent (n = 107)** | | | |
| Positive slope | 52 (48.6%)<br>2 (1 - 4) | 22 (20.6%)<br>3 (2 - 4) | 4 (1.9%)<br>0 (0 - 0.5) |
| Negative slope | 11 (10.3%)<br>1 (1 - 3) | 18 (16.8%)<br>3 (3 - 4) | |
| **Good (n = 31)** | | | |
| Positive slope | 12 (38.7%)<br>1.5 (1 – 3.5) | 8 (25.8%)<br>2.5 (2 - 4) | 0 |
| Negative slope | 6 (19.4%)<br>1.5 (1 - 2) | 5 (16.1%)<br>3 (2 – 3) | |
| **Modest (n = 31)** | | | |
| Positive slope | 14 (45.2%)<br>2 (2 – 3) | 5 (16.1%)<br>3 (0 – 5) | 1 (3.2%)<br>0 ( 0 – 0) |
| Negative slope | 6 (19.4%)<br>3 (0 – 4) | 5 (16.1%)<br>2 (1 – 3) | |
| **Poor (n = 15)** | | | |
| Positive slope | 6 (40.0%)<br>3 (1 – 4) | 2 (13.3%)<br>5 (3 – 7) | 0 |
| Negative slope | 0 | 7 (46.7%)<br>3 (3 – 5) | |
| **No stable gain (n = 19)** | | | |
| Positive slope | 4 (21.1%)<br>(4.5 – 2.0) | 4 (21.1%)<br>3 (2.5 – 3.5) | 1 (5.3%)<br>2 (2 – 2) |
| Negative slope | 4 (21.1%)<br>1.5 (0.5 – 2.0) | 6 (31.6%)<br>2.5 (1 – 4) | |
| **Missing (n = 4)** | | | |
| Positive slope | 0 | 0 | 2 (50.0%)<br>0 (0 – 0) |
| Negative slope | 0 | 2 (50.0%)<br>3 (2 – 4) | |
| **Total (n = 207)** | | | |
| Positive slope | 88 (42.5%)<br>2 (1 – 4) | 41 (19.8%)<br>3 (2 – 4) | 8 (3.9%)<br>0 (0 – 0.5) |
| Negative slope | 27 (13.0%)<br>2 (1 – 3) | 43 (20.8%)<br>3 (2 – 4) | |

a: Week 16 to Week 24
b: Week 24 to Week 52

On the other hand, about 61% (43 of 70 [27+43] subjects) of the subjects who demonstrated a negative slope in the fixed dosing phase experienced a continued decline during the PRN dosing phase while receiving a median of 3 active injections. Conversely, about 38% of subjects who demonstrated a negative slope in the fixed dosing phase experienced an improvement (or no change) during the PRN dosing phase, while receiving a median of 2 active injections.

Taken together, these data would appear to confirm that it was largely possible to maintain the gains achieved in the first 6 months through the end of the second 6 months. There is no clear trend in terms of the number of injections administered. Overall, subjects receiving fewer injections and those receiving more injections in the PRN phase both show deterioration of as well as improvements in BCVA. However, because many of the groups displayed in Table 12 are relatively small, any conclusions must be drawn with caution.

*Table 13 shows the comparison between slopes at the end of the fixed dosing phase (Weeks 16 to 24) and the slope of the change in BCVA through the end of the studies (Week 76/100).*

**Table 13: Integrated analysis. BCVA behaviour in the fixed dosing phase versus the reactive dosing (Week 24 to Week 76/100) phase by stability categories achieved with fixed dosing (subjects completing Week 24).**

| | Each cell presents:<br>**Number** of subjects<br>**Median (Q1 – Q3)** number of injections in the PRN phase | | |
|---|---|---|---|
| **Fixed-dosing phase stability category[a] BCVA behavior** | **Reactive PRN-dosing phase[b] BCVA behavior** | | |
| | **Improvement** | **Decline** | **Missing**<br>N () |
| **Excellent (n = 107)** | | | |
| Positive slope | 46 (43.0%)<br>3.5 (2 – 6) | 28 (26.2%)<br>6 (5 – 8) | 4 (1.9%)<br>0 (0 – 0.5) |
| Negative slope | 10 (9.3%)<br>3.5 (1 – 5) | 19 (17.8%)<br>6 (5 – 7) | |
| **Good (n = 31)** | | | |
| Positive slope | 11 (35.5%)<br>5 (1 – 8) | 9 (29.0%)<br>5 (4 – 8) | 0 |
| Negative slope | 3 (9.7%)<br>1 (0 – 1) | 8 (25.8%)<br>5 (4 – 7.5) | |
| **Modest (n = 31)** | | | |
| Positive slope | 13 (41.9%<br>4 (3 – 5) | 6 (19.4%)<br>4 (0 – 8) | 1 |
| Negative slope | 3 (9.7%)<br>0 (0 – 1) | 8 (25.8%)<br>5 (2.5 – 8.5) | |
| **Poor (n = 15)** | | | |
| Positive slope | 6 (40.0%)<br>3 (2 – 5) | 2 (13.3%)<br>7 (4 – 10) | 0 |
| Negative slope | 1 (6.7%)<br>6 (6 – 6) | 6 (40.0%)<br>6.5 (4 – 8) | |
| **No stable gain (n = 19)** | | | |
| Positive slope | 3 (15.8%)<br>9 (4 – 9) | 5 (26.3%)<br>7 (5 – 7) | 1 |
| Negative slope | 3 (15.8%)<br>3 (3 – 4) | 7 (36.8%)<br>5 (0 – 8) | |
| **Missing (n = 4)** | | | |
| Positive slope | 0 | 0 | 2<br>0.5 (0 – 1.0) |
| Negative slope | 1 ((25%)<br>10 (10 – 10) | 1 (25%)<br>4 (4 – 4) | |
| **Total (n = 207)** | | | |
| Positive slope | 79 (38.2%)<br>4 (2 – 6) | 50 (24.2%)<br>5.5 (4 – 8) | 8 (3.9%)<br>0 (0 – 1.0) |
| Negative slope | 21 (10.1%)<br>3 (1 – 5) | 49 (23.7%)<br>6 (4 – 7) | |

a: Week 16 to Week 24
b: Week 24 to Week 52

[NB - Evaluator comment: The superscript "b" for Table 13 appears to relate to Week 2*4 to Week 76/100*, not Week 2*4 to Week 52* as stated immediately under the Table in the sponsor's Response.]

A total of 129 subjects demonstrated a positive slope in the fixed dosing phase, of which 39% (50 subjects) experienced a decline in BCVA during the PRN dosing phase. This is a deterioration from Week 52 where the decline was 32%. Conversely, about 61% (79 subjects) who demonstrated a positive slope in the fixed dosing phase experienced an improvement (or no change) in BCVA during the PRN dosing phase, thus fewer subjects than at Week 52 where the number was 68%.

On the other hand, of the 70 subjects who demonstrated a negative slope in the fixed dosing phase, 70% (49 subjects) experienced a continued decline during the as needed treatment phase, again a deterioration compared to only 61% at Week 52. Conversely, about 30% (21 subjects) who demonstrated a negative slope in the fixed dosing phase experienced an improvement (or no change) during the PRN dosing phase. This number was also better at Week 52 with 39%.

Taken together, these data would appear to confirm that the slightly negative trend seen between Week 24 to 52 is further enhanced with extension of the monitoring intervals under a reactive treatment regimen up to Week 76/100.

Again, there is no clear trend in terms of the number of injections administered. Overall, subjects receiving fewer injections and those receiving more injections in the PRN phase both show deterioration of as well as improvements in BCVA. However, because many of the groups displayed in Table 13 are relatively small, again any conclusions must be drawn with caution.

***Conclusion of the findings from the Integrated Analysis including the complete 76/100 week data***

The GALILEO and COPERNICUS studies have shown that VEGF Trap-Eye treatment resulted in fast and sustainable gains in visual acuity. Most of the treatment effect is established early and stability is reached in the majority of patients after the first 3 injections. The studies have shown that the efficacy gains were maintained even under an extended treatment interval after the initial monthly dosing phase. The studies have furthermore demonstrated that the success of a PRN regimen is very much contingent on monthly monitoring.

During the entire study period treatment, the overall incidence of ocular and non ocular TEAEs and SAEs of interest was similar between treatment groups. Overall, the incidence of subjects experiencing the non ocular TEAE of interest of Hypertension was similar between treatment groups and did not suggest a relationship between this AE and treatment. Similarly, no association was observed between APTC events and treatment.

As noted also in the sponsor's response provided previously to Efficacy (b), it is apparent from the in depth analysis provided that mismatches between retreatment and treatment criteria and treatment affects about one third of patients over the full study duration of GALILEO and COPERNICUS. This demonstrates that the subjects tend to be under treated more often than over treated even under controlled study conditions. Such under treatment presents a potential downfall for the PRN dosing regimen that is evaluated in the studies. This potential risk of under treatment might become more severe when controlled study conditions are exchanged for real life situations in clinical practice, leading to destabilisation of disease condition.

***Proposed changes to the recommended dosage regimen***

Based on all of the above, the sponsor hereby proposes to translate the findings of the studies into a "treat-and-extend" label, where the treatment interval may be extended based on visual and anatomic outcomes.

The following recommended dosage regimen for the treatment of macular oedema following CRVO was proposed in the present sponsor's response:

> "*Eylea treatment is performed with one intravitreal injection per month for three consecutive doses.*
>
> *The treatment interval may then be extended beyond one month based on visual and anatomic outcomes*."

The sponsor considered that the above proposed posology allowing a "treat-and-extend" schedule compensate the potential weakness of the PRN re treatment criteria. The potential risk of under treatment is also mitigated as the decision on the extension of the treatment interval depends on the overall visual and anatomic outcomes assessed by the physician. If after the initial three consecutive doses at monthly interval, the physician considers that the patient condition is not adequately stabilised clinically to warrant an extension in the treatment interval, the physician can continue to provide continual treatment to the patient at monthly interval thereafter based on clinical assessment at each subsequent visits.

Following comment from the evaluator on the sponsor's proposal for a "treat-and-extend" posology after three initial monthly doses for the treatment of macular oedema following CRVO, an update to the proposed PI *Dosage and Administration* will be provided as part of the sponsor's comments on the Round 2 CER.

*Evaluator's comment*

The revised 'treat and extend' dosage regimen has not been tested in a pivotal Phase III study specifically designed to evaluate its efficacy. In the two pivotal Phase III studies submitted by the sponsor (COPERNICUS and GALILEO), the primary efficacy endpoint was the proportion of subjects gaining ≥15 letters at Week 24 following monthly IVT injections of Eylea (2 mg) (that is, dosing at Weeks 0, 4, 8, 12, 16 and 20). From Week 24 to Week 52, both studies adopted a PRN approach to re treatment with aflibercept based on monthly evaluation and protocol specified re treatment criteria, while from Week 52 to Week 100 in COPERNICUS the PRN approach to treatment with aflibercept was continued based on quarterly evaluation and protocol specified re treatment criteria and from Week 52 to 76 in GALILEO and the PRN approach to treatment with aflibercept was continued based on assessment every 8 weeks and protocol specified re treatment criteria. The designs of the two pivotal studies are outlined below in Figures 4 and 5.

**Figure 4: Copernicus – Study design.**

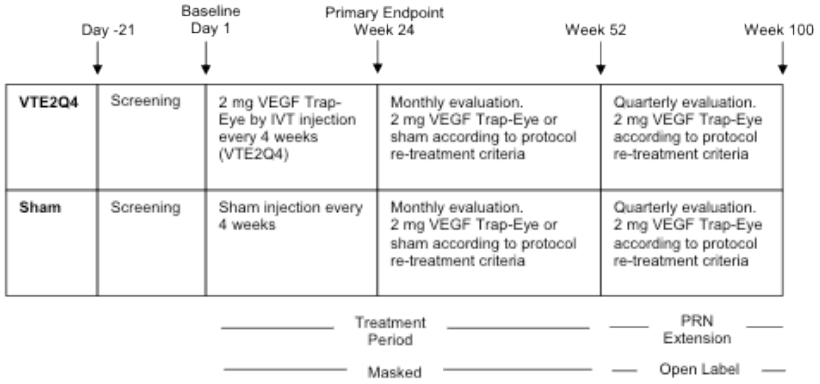
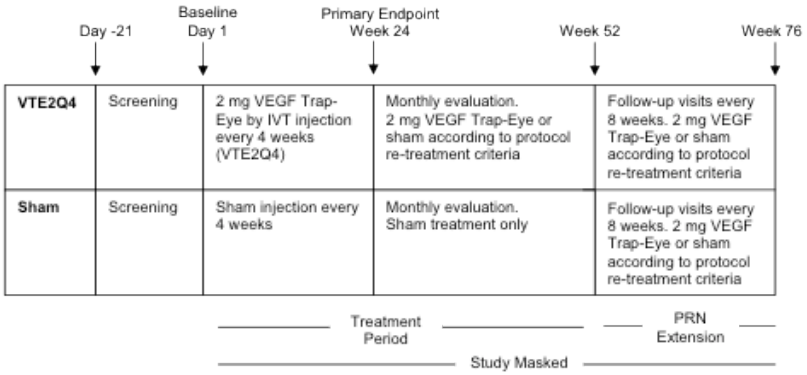



**Figure 5: GALILEO – Study design.**




The initial assessment of the two pivotal studies suggested that treatment should be initiated with 6 injections administered at monthly intervals. However, the optimal dosing regimen from Week 24 onwards was unclear with the options being: (i) a reactive PRN regimen with assessment at monthly intervals from Week 24 to Week 52 and at two to three monthly intervals from Week 52 with re treatment at each assessment time point being according to specified re treatment criteria consistent with those in the pivotal studies; (ii) a proactive regimen with monthly injections; or (iii) a proactive regimen with injection every two months. Overall, it is considered that the originally submitted data best

supported initiation of treatment with 6 injections at monthly intervals followed by the reactive PRN regimen.

However, the sponsor's response suggests that it now considers that initial treatment with 6 injections at monthly intervals might be over treatment as there was little change in BCVA of ≥ 15 letters from Week 12 (that is, following 3 monthly injection) to Week 24 (that is, following 6 monthly injections) in the integrated assessment of the COPERNICUS and GALILEO data. Furthermore, the sponsor's response suggests that it considers that PRN treatment based on fixed-assessment periods might result in under treatment. The sponsor refers to data from COPERNICUS and GALILEO showing that mismatches between re treatment criteria and treatment affects about one third of subjects over the full duration of the studies. Of the subjects completing the fixed-dose period, 33.3% (33/99) in the PRN group (following sham, after first PRN) and 34.8% (72/207) in the VTE2Q4+PRN group experienced at least one mismatch between injections and re treatment criteria (see Table 14, below).

**Table 14: Proportion of subjects with matches/mismatches between injections and retreatment criteria from end of fixed dose to Week 76/100 on scheduled and unscheduled visits combined (subjects completing fixed dose)**

| | PRN (following sham, after 1st PRN) N=99 (100%) | VTE 2Q4 + PRN N=207 (100%) |
|---|---|---|
| Number of subjects who discontinued study medication during fixed dose | 0 | 3 ( 1.4%) |
| Number of subjects with total match between active injections and retreatment criteria [a] | 66 ( 66.7%) | 132 ( 63.8%) |
| Number of subjects with at least one mismatch between injections and retreatment criteria | 33 ( 33.3%) | 72 ( 34.8%) |
| At least one retreatment criterion fulfilled, but no active injection | 21 ( 21.2%) | 69 ( 33.3%) |
| No retreatment criterion fulfilled, but active injection | 13 ( 13.1%) | 10 ( 4.8%) |

Note: VTE 2Q4+PRN: VEGF Trap-Eye (VTE) administered at 2 mg every 4 weeks from day 1 to week 20 followed by administration as needed (PRN).
Note: PRN (following sham, after 1st PRN): includes all subjects receiving at least one active PRN injection and considers time period from 1st active PRN injection onwards.
Note: For the purpose of this table fixed dose period (up to week 24) includes Galileo sham period up to week 52.
Injections at unscheduled visits are counted.
Note: Injections are excluded when no retreatment criteria are available.
[a] Total match: For all visits active injection was given if any retreatment criterion was fulfilled and no active injection was given if no retreatment criterion was fulfilled.

The sponsor postulated that the "*potential risk of under-treatment might become more severe when controlled study conditions are exchanged for real-life situations in clinical practice, leading to destabilization of disease condition*". The sponsor discussed their concern about under treatment with a PRN regimen and the potential for disease destabilisation with such a regimen in the original submission (*Justification for Recommended Posology*). The sponsor's concerns about the PRN regimen was one of the main reasons for the sponsor initially proposing a fixed dose regimen of aflibercept (2 mg) every two months to follow the initial fixed dose regimen of aflibercept (2 mg) every month for six injections. The other main reason stated by the sponsor in the original submission for the fixed dose regimen from Month 24 was that a PRN regimen "*appeared no more efficacious or safe than the consistent proactive dosing used in the first 6 months of the [pivotal] studies*".

In the revised treatment regimen, following the initial regimen of 1 injection each month for three months for all patients, the sponsor has proposed an individualised PRN regimen based on variable time periods for assessment and re treatment. However, it is unclear how the revised PRN regimen addresses the sponsor's concerns regarding PRN treatment expressed in the initial submission. The minimum time interval between assessments and potential re treatments in the PRN phase appears to be one month and can be increased based on visual and anatomic outcomes. The sponsor postulates that the disease will be treated proactively at most visits with the "*treat and extend paradigm*", while "a*t the same time the treatment interval is adjusted to avoid over- or under-treatment and also ascertains that patient safety is well controlled*". It is unclear how the proposed "*treat and extend paradigm*" can be considered to be proactive when treatment will be triggered "reactively" by assessment of visual and anatomic outcomes at each assessment. A proactive regimen implies fixed dose treatment undertaken at fixed intervals with the aim of maintaining disease stability without deterioration between treatments.

Overall, it is considered that introducing a markedly revised treatment regimen at this stage of the evaluation process raises uncertainty about the optimal dosing regimen for the proposed indication. The sponsor has raised serious concerns about the dosing regimen it initially proposed for approval. It is considered that these concerns can only be addressed by a pivotal Phase III study evaluating the proposed dosing regimen for the proposed indication, or (at the very least) a comprehensive justification of the proposed dosing regimen. Such a justification should take the form of the detailed and comprehensive "*Justification for the Recommended Posology*" document included in the original submission. The justification should comprehensively compare and analyse the primary and secondary efficacy outcomes at Week 12 (that is, after the first 3 injections at Weeks 0, 4 and 8) and Week 24 (that is, after the first 6 injections at Weeks 0, 4, 8, 12, 16 and 20) separately in both pivotal studies and in an integrated analysis of both studies. In addition, the justification should also examine the primary and key secondary endpoints using the methodology described in the sponsor's response to compare the outcomes in the fixed dosing phase with the reactive dosing phase separately for each pivotal Phase III study and in the integrated database of both studies.

### Second round recommendation regarding authorisation

The sponsor's proposal to revise the initially proposed dosage regimen gives rise to significant uncertainty relating to the optimal dosing regimen for aflibercept for the proposed indication. In particular, the sponsor has expressed concerns about the potential of the dosage regimen it initially proposed to potentially over treat or under treat the condition.

The dosage regimen recommended by the clinical evaluator is provided immediately below and is consistent with the regimens tested in the two pivotal Phase III studies:

> *An initial fixed-dose regimen of one injection a month for six months (that is, a total of 6 injections);*
>
> *followed by a PRN once monthly re-treatment regimen from Week 24 to Week 52 based on re-treatment criteria consistent with those in the pivotal studies (that is, regular assessment at monthly intervals);*
>
> *followed by a PRN once every two or three months regimen from Week 52 onwards based on re-treatment criteria consistent with those in the pivotal studies (that is, regular assessment at two to three month intervals).*

However, the data in sponsor's response to *Dosing Regimen Question f* (see above) suggests that the clinical evaluator's recommended treatment regimen has the potential to over treat in the initial fixed dose phase and under treat in the subsequent reactive PRN treatment phase.

In the absence of a comprehensive review of the efficacy data comparing and analysing initial 3 and 6 injection fixed dose monthly injection regimens and outcome data comparing the initial fixed-dose regimen (Week 0 to 24) with the subsequent reactive regimen (Week 24 through to study end), it is not possible to make a meaningful benefit-risk assessment of the revised treatment regimen.

Consequently, it was recommended that the submission to extend the indication of aflibercept for the treatment of macular oedema following central retinal vein obstruction be rejected on the grounds of inadequate demonstration of the efficacy of the proposed revised 'treat and extend' regimen. The provided data relating to BCVA ≥ 15 letters suggests that the proposed revised 'treat and extend' regimen might reduce the risk of over treatment in the initial fixed dose phase and potentially reduce the risk of under or over treatment in the subsequent reactive PRN phase compared with the sponsor's

initially proposed treatment regimen. However, adequate confirmatory data satisfactorily establishing the efficacy of the proposed revised regimen compared with the initially proposed regimen is required.

# V. Pharmacovigilance findings

## Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

### Safety specification

The sponsor provided a summary of ongoing safety concerns and it is shown in Table 15 below.

**Table 15: Summary of ongoing safety concerns**

| | |
|---|---|
| Important identified risks: | Endophthalmitis<br>Transient intraocular pressure increase<br>Conjunctival hemorrhage<br>Eye pain<br>Vitreous detachment<br>Vitreous floaters<br>Retinal pigment epithelium tears |
| Important potential risks: | Hypersensitivity and immunogenicity<br>Traumatic cataract<br>Arterial thromboembolic events including non-MI ATEs and cardiovascular ischemic events<br>Venous thromboembolic events<br>Hypertension<br>Proteinuria<br>Non-ocular hemorrhage<br>Medication error<br>Off-label use<br>Embryo-fetotoxicity<br>Retinal hemorrhage |
| Important missing information: | Use of Eylea® in patients with uncontrolled glaucoma<br>Concomitant use of different anti-VEGF therapies and other therapies for wet AMD<br>Long term safety beyond 2 years<br>Posology utilized in marketed use |

### Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities to address the important identified and important potential risks. Additional pharmacovigilance activities include post authorisation safety studies (PASSs) and a long term safety extension study which will be conducted in Europe.

Additional pharmacovigilance activities proposed by the sponsor include follow up questionnaires for events relating to the identified risks of Endophthalmitis, Hypertension and Arterial thromboembolic events.

The proposed and ongoing studies are not conducted in Australia and safety related events will be communicated to the TGA in Periodic Safety Update Reports (PSURs) and

any updated version of the EU RMPs. The reporting milestones were considered to be acceptable.

### Risk minimisation activities

The proposed risk minimisation plan for the Australian market includes routine as well as additional pharmacovigilance activities and routine risk minimisation activities.

Additional pharmacovigilance activities conducted in Australia include follow up questionnaires for events relating to the identified risk of Endophthalmitis, Hypertension and Arterial thromboembolic events.

Additional pharmacovigilance activities (PASSs and extension trial VGT-OD-0910) and additional risk minimisation activities (patient education and physician education) are proposed for the European market only.

It was recommended by the evaluator that additional risk minimisation activities be conducted by the sponsor. These activities should be aimed at:

1. Preventing medication errors due to form of presentation of the product,
2. Educating the patients about their treatment.

### Reconciliation of issues outlined in the RMP report

Table 16 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

**Table 16: RMP Round 1 evaluation, sponsor's response and RMP Round 2 evaluation.**

| Recommendation in RMP evaluation report | Sponsor's response | OPR evaluator's comment |
|---|---|---|
| 1. It was recommended that the sponsor submits study reports resulting from the PASS, completed and ongoing clinical trials to the TGA at the same time as reports are submitted to other regulatory agencies. | The sponsor provided an assurance that the study reports from the PASS, completed and ongoing clinical trials referenced in the EU-RMP will be submitted to the TGA in the same timeframe as the reports submitted to other regulatory agencies. | The response was considered acceptable by the Round 2 RMP evaluator. |
| 2. It was recommended that the sponsor provides the "intravitreal injections information sheet and consent form" and "Instructions for patients following intravitreal injection" to the TGA for review prior to approval. | The documents entitled "Intravitral injections Information Sheet and Consent Form" and "Instructions for patients following intravitreal injection" developed by RANZCO were provided to the TGA. | The information which was requested in the Round 1 RMP report has been received by the TGA.<br>It was considered by the RMP evaluator that this document does not provide sufficient information (please refer to point 4 in this table). |
| 3. It was recommended the wording in the PI be changed. Wording in the currently proposed PI: | The sponsor accepted the OPR recommendation and provide an assurance that the wording in the PI would be revised as annotated | The response and the proposed amendment to the PI were considered acceptable by the Round 2 |

| Recommendation in RMP evaluation report | Sponsor's response | OPR evaluator's comment |
|---|---|---|
| *Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal/injections.*<br><br>Recommended wording: *Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified ophthalmologist experienced in administering intravitreal injections.* | below:<br><br>"*Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified ophthalmologist experienced in administering intravitreal injections."*<br><br>The revised PI will be provided to the TGA with our response to the Round 2 CER. | RMP evaluator. |
| 4. It was recommended that the sponsor provides patient educational materials | As stated in the ASA (Version 1.0) submitted with our application, the sponsor does not consider it necessary to provide patient education material as a risk minimisation measure for the use of Eylea in Australia. | The RMP evaluator acknowledged the response from the sponsor. However, the RMP evaluator maintained the strong position that the sponsor should generate educational materials for patients, as discussed in the Round 1 RMP evaluation, which are same/similar to the one distributed in Europe. |
| 5. To prevent medication errors it was recommended that the sponsor undertakes further risk minimisation activities, this could include but is not limited to: A label clearly indicating the required injection volume on the glass vial or on the syringe. | The sponsor evaluated the OPR's concern for potential medication error to occur due to the difference in the extractable volume from the product and the actual volume needed for injection, and has considered that no further risk minimisation activities are required. This is based on the rationale provided herein.<br><br>Each glass vial / prefilled syringe unit contains only the minimum fill volume that is required to deliver one single dose of Eylea (50 µL). The minimum fill volume for the prefilled syringe and glass vial has been carefully determined during the pharmaceutical development of the product, and the extractable | The RMP evaluator acknowledged the necessity for providing a higher volume than required, to ensure that a single dose (50 µL) can be reproducibly administered by treating ophthalmologists.<br><br>The sponsor described under the last dot point of the response (please refer to sponsor's response to the left): *it would not be possible to <u>reproducibly</u> administer more than one single dose from each glass vial or prefilled syringe.* In the opinion of the RMP evaluator this statement implicates that medication |

| Recommendation in RMP evaluation report | Sponsor's response | OPR evaluator's comment |
|---|---|---|
| | volume for the prefilled syringe and glass vial has also been evaluated by the Administration during the original registration application of Eylea. The apparent excess in the extractable volume compared to the actual volume needed for injection was considered in the final CMC Evaluation as acceptable based on the following justifications:<br>• The excess contained in the extractable volume in the glass vial (100 µL) and prefilled syringe (90 µL) is required to compensate for the "priming volume" (that is, the volume required to expel all the air from the syringe and properly prime the needle prior to administering the intravitreal injection), and the "average dead volume of the syringe and needle" in order to deliver the volume dose of 50 µL required for administration when the product is administered according to the recommended instructions provided in the labelling.<br>• The extractable volume in both the glass vial and prefilled syringe is determined using the current European Pharmacopiea (Ph. Eur) procedure and represents the minimum extractable volume necessary to enable the end user to remove the required volume of solution (50 µL) for a single dose.<br>• From the user testing that has been performed during pharmaceutical development, it is evident that based on the minimum fill volume contained in the glass vial and prefilled syringe, it | error can occur.<br>The RMP evaluator maintains the position that there is potential for medication error. This risk can be minimised by amending the package and/or amending the vial/PFS label, by clearly indicating, that the volume required for injection differs from the total volume provided.<br>Alternatively, educational material informing treating physicians about the posology of the product may be distributed by the sponsor. |

| Recommendation in RMP evaluation report | Sponsor's response | OPR evaluator's comment |
|---|---|---|
| | would not be possible to reproducibly administer more than one single dose from each glass vial or prefilled syringe. | |

**Summary of recommendations**

It was considered that the sponsor's response to the TGA request for information did not adequately addressed all of the issues identified in the RMP evaluation report (see *Outstanding issues* below)

***Outstanding issues***

*Issues in relation to the RMP*

1. It was recommended to the Delegate that the sponsor generates educational materials for patients, as discussed in the Round 1 RMP evaluation, which are the same/similar to the material distributed in Europe. If this is to be implemented the sponsor has to ensure that this is reflected in the Australian Specific Annex to the EU RMP.
2. It was recommended to the Delegate that the sponsor amends the package and/or amends the vial/pre-filled syringe label, by clearly indicating, that the volume required for injection differs from the total volume provided.

Alternatively, educational material informing treating physicians about the posology of the product may be distributed by the sponsor.

***Suggested wording for conditions of registration***

*RMP*

Implement EU RMP, Version 8.0 (dated 30 October 2012) with Australian Specific Annex to the EU RMP Version 8.0, Version 1.0 (dated November 2012) and any future updates as a condition of registration.

*PSUR*

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module Vll-Periodic Safety Update Report, Part Vll. B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

# VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

There was no requirement for a quality evaluation in a submission of this type.

### Nonclinical

The non-clinical evaluator had no objections to the registration of aflibercept for the indication of macular oedema following CRVO.

### Clinical

The clinical evaluator had no concerns about the efficacy and safety of aflibercept as dosed in the two pivotal trials (GALLIEO and COPERNICUS): 1 monthly injection for 6 months and then PRN based on assessment at fixed, scheduled monitoring visits (see Table 18, below). The main problem identified by the clinical evaluator was how to translate the somewhat artificial dosage regimen used in the pivotal trials to the real-world of everyday clinical practice (see further discussion below).

### Pharmacology

No new pharmacodynamic (PD)/pharmacokinetic (PK) properties were identified beyond those already identified for already registered indication of neovascular age-related macular degeneration.

In the mandatory PK assessment (GALILEO), repeat administration of aflibercept resulted in free trough plasma concentrations that were below the lower limit of quantification (LLOQ) in all subjects. Repeated administration of aflibercept 2 mg every 4 weeks through to Week 24 and then as required (PRN) up to Week 52 did not result in accumulation of the drug in plasma. Therefore, the PK results suggest no increased risk of systemic side effects with VTE following long term treatment.

Exploratory sub group analyses with respect to age, sex, body mass index (BMI), creatinine clearance, hepatic impairment and geographical region could not be conducted because all free VTE plasma trough concentrations were below the LLOQ.

Adjusted aflibercept bound trough plasma concentrations increased from baseline (pre dose) to Week 24; after which concentrations decreased through to Week 52. None of the sub group analyses resulted in noteworthy differences between subjects and subject numbers in some sub groups were too small for meaningful comparisons to be made (for example, hepatic impairment, moderate and severe renal impairment, and subjects aged ≥ 75 years).

Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. It is expected to be eliminated through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. No dose adjustment for renal impairment is needed.

## Efficacy

**Table 17: Study characteristics. GALLIEO & COPERNICUS (Phase III, pivotal evidence provided for efficacy claim)**

| | |
|---|---|
| **Patients** | Treatment-naïve, 18+ years (mean=62 years), women: 44%<br>CRVO for a maximum of 9 months (<2 months: 53%, 2+ months: 47%)<br>Central retinal thickness > 250um on optical coherence tomography<br>Best corrected visual acuity (BCVA) of 73 to 24 letters (20/40 to 20/320)<br>ETDRS BCVA > 20/200: 83%<br>Exclusions: uncontrolled glaucoma, filtration surgery, bilateral RVO, iris neovascularisation, prior treatment with anti-VEGF agents, panretinal or macular laser photocoagulation, intraocular corticosteroids.<br>GALLIEO: n=177 (3:2, aflibercept: 106; sham: 71) |
| **Intervention** | Aflibercept 2mg intravitreal injection. Pan-retinal photocoagulation was allowed at any time for all patients (including those in the sham group) if they progressed to neovascularisation of the anterior segment, optic disc, or fundus. (see Table below, for dosing schedule) |
| **Comparator** | Sham procedure |
| **Design** | See Table below |
| **Primary endpoint** | Percentage of patients who gained 15+ letters in best corrected visual acuity (BCVA) at Week 24 compared to baseline. (3-line gainers) |
| **Secondary endpoints** | Mean change in BCVA and CRT at Week 24<br>Progression to neovascularisation of anterior segment, optic disc or elsewhere on fundus at Week 24<br>Changes in quality of life (QoL) |
| **Follow-up** | See Table 18 below |
| **Minimal clinically important difference used in sample size calculation** | 25% difference between the 2 groups in the percentage of 3-line gainers. |

**Table 18: Follow-up Schedule**

| | COPERNICUS | | GALILEO | |
|---|---|---|---|---|
| | **Intervention arm** | **Control arm** | **Intervention arm** | **Control arm** |
| **0-24 weeks** | Monthly injection of aflibercept | Monthly sham injection | Monthly injection of aflibercept | Monthly sham injection |
| **25-52 weeks**<br>**(PRN dosing, based on monthly monitoring)** | Monthly evaluation:<br>aflibercept or sham injection according to retreatment criteria | Monthly evaluation:<br>aflibercept or sham injection according to retreatment criteria | Monthly evaluation:<br>aflibercept or sham injection according to retreatment criteria | Monthly evaluation:<br>sham injection only |
| **53-100 (COPERNICUS)**<br>**53-76 (GALILEO)**<br>**(PRN dosing, based on 3/2 monthly monitoring)** | 3-monthly evaluation:<br>aflibercept according to retreatment criteria | 3-monthly evaluation:<br>aflibercept according to retreatment criteria | 2-monthly evaluation:<br>aflibercept or sham injection according to retreatment criteria | 2-monthly evaluation:<br>aflibercept or sham injection according to retreatment criteria |

Retreatment criteria: >50 µm increase in central retinal thickness (CRT) on OCT compared with lowest previous measurement. Persistent cystic retinal changes.
Subretinal fluid on OTC. Oedema >200 µm in the central subfield on OCT. Loss >5 letters from best prior measurement with any increase in CRT on OCT

### *Summary of treatment schedule in COPERNICUS and GALILEO after 24 weeks (see Table 18, above)*

From 25-52 weeks, all patients in COPERNICUS received aflibercept or sham depending on retreatment criteria at scheduled 1 monthly monitoring (PRN dosing); that is, both groups got the same intervention. In GALILEO, patients in the sham arm continued to get sham injections.

From 53 to 100 weeks, all patients in COPERNICUS got aflibercept depending on retreatment criteria at 3 monthly monitoring (PRN dosing).

From 53 to 76 weeks, all patients in GALILEO got aflibercept depending on retreatment criteria at 2 monthly monitoring (PRN dosing).

**Table 19: Efficacy outcomes at 24 weeks, GALILEO & COPERNICUS**

| | GALILEO | | COPERNICUS | | POOLED | |
|---|---|---|---|---|---|---|
| | Sham (n=68) | Aflibercept (n=103) | Sham (n=73) | Aflibercept (n=114) | Sham (n=141) | Aflibercept (n=217) |
| Primary Gained 15 letters | 15 (22%) | 62 (60%) | 9 (12%) | 66 (58%) | 24 (17%) | 131 (60%) |
| Secondary Mean change in central retinal thickness | -169.27 | -448.58 | -144.8 | -457.2 | -157.2 | -453.1 |

**Table 20: Percent 3-line gainers at Week 24, 52, 76/100, COPERNICUS, GALILEO, (full analysis set with LOCF). S=Sham and Af= Aflibercept**

| | COPERNICUS | | | | | | GALILEO | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 24 weeks | | 52 weeks | | 100 weeks | | 24 weeks | | 52 weeks | | 100 weeks | |
| n | S 73 | Af 114 | S 73 | Af 114 | S 73 | Af 114 | S 68 | Af 103 | S 68 | Af 103 | S 68 | Af 103 |
| Gained 15 letters (%) | 12 | 56 | 30 | 55 | 23 | 49 | 22 | 60 | 32 | 60 | 29 | 57 |
| wt'd difference (95% CI) p-value | 45% (33%, 57%) p<0.001 | | 26% (12%, 40%) p<0.001 | | 27% (13%, 40%) p<0.001 | | 38% (24%, 52%) p<0.001 | | 28% (13%, 43%) p<0.001 | | 28% (13%, 43%) p<0.001 | |

**Table 21: Comparison of efficacy outcomes at 12 and 24 weeks**

| | | GALILEO | | COPERNICUS | | POOLED | |
|---|---|---|---|---|---|---|---|
| | | Sham n=68 | Aflib. n=103 | Sham n=73 | Aflib. n=114 | Sham n=141 | Aflib. n=217 |
| Gained 15 letters (1) | Week 12 | 8 (12%) | 60 (58%) | 7 (10%) | 64 (56%) | 15 (11%) | 126 (58%) |
| | Week 24 | 15 (22%) | 62 (60%) | 9 (12%) | 66 (58%) | 24 (17%) | 131 (60%) |
| mean change in BVCA (2) | Week 12 | 1.7 | 16.5 | -4.2 | 16.7 | -1.4 | 16.6 |
| | Week 24 | 3.3 | 18.0 | -4.0 | 17.3 | -0.5 | 17.7 |

| | | GALILEO | | COPERNICUS | | POOLED | |
|---|---|---|---|---|---|---|---|
| mean change in central retinal thickness (2) | Week 12 | -101.52 | -442.18 | -75.1 | -441.4 | -88.5 | -441.8 |
| | Week 24 | -169.27 | -448.58 | -114.8 | -457.2 | -157.2 | -453.1 |

1. Primary endpoint
2. Secondary endpoints

*Comment:* Most gains observed at 24 weeks were already gained by 12 weeks.

### Safety

Aflibercept is already registered for neovascular (wet) age-related macular degeneration. No new safety concerns have emerged from the development program for the indication being considered in this application (macular oedema secondary to CRVO).

The safety population for neovascular age-related macular degeneration consisted to 2141 patients; the safety population for macular oedema secondary to CRVO consisted of 317 patients. The most common adverse reactions (>5%) were conjunctival haemorrhage, increased intra-ocular pressure, eye pain, vitreous detachment, vitreous floaters, increased lacrimation and ocular hyperaemia. The current PI contains precautions about endophthalmitis and increased intraocular pressure.

The PI states that Eylea "*must only be administered by a qualified physician (RMP evaluation report requested a change to ophthalmologist) experienced in administering intravitreal injections*."

## Risk management plan

Implement EU RMP, Version 8.0 (dated October 2012) with Australian Specific Annex to the EU RMP Version 8.0, Version 1.0 (dated November 2012).

## Risk-benefit analysis

### Delegate considerations

Two Phase III trials show that aflibercept is, on average, of benefit to patients with macular oedema secondary to CRVO; although the response of individual patients is variable and treatment needs to be tailored to individual patients. The safety profile is acceptable; the treatment should only be delivered by specialist physicians/ophthalmologists. Pending ACPM advice, the Delegate had no reason to say, at this time, that the application for extension of indications for Eylea should not be approved for registration.

### Specific question for ACPM on dosage and administration

The key issue for this application is the recommendation for the "*Dosage and Administration*" section of the PI.

Although suitable for a clinical trial, the dosage regimen used in the two pivotal trials (pre-specified, scheduled monitoring with PRN injections) is not feasible for everyday clinical practice and would be a burden for patients.

### *Proposed dosing in Australia*

The application initially proposed:

- one intravitreal injection (that is, 50 µL, equivalent to 2 mg of aflibercept) per month for the first six months, followed by one intravitreal injection (that is, 50 µL, equivalent to 2 mg of aflibercept) every two months.

The clinical evaluator asked the sponsor to comment on why 2 monthly injections from 6 months onwards had been proposed rather than continuing with 1 monthly injections.

In response, the sponsor then proposed a 'treat and extend' regimen, that is, one injection per month for 3 consecutive doses; the treatment interval may then be extended beyond one month based on visual and anatomic outcomes. This was similar to amendments made as part of the application to the EU (see next section, below).

The evaluator then recommended rejection because the "extend-and-treat" regimen had not been evaluated in the two pivotal trials (GALLIEO and COPERNICUS).

The sponsor then proposed the following indication:

*Eylea treatment is initiated with one intravitreal injection per month for six consecutive months.*

- *After the first three injections, consideration may be given to continue treatment at monthly intervals or with an extended treatment interval based on visual and anatomic outcomes.*
- *The interval between doses should not be shorter than one month.*
- *If visual acuity or anatomic outcomes indicate no benefit of therapy over the course of the first three injections, continued treatment is not recommended.*
- *Monitoring should be done at the injection visits. During treatment extension through to completion of therapy, the monitoring schedule is determined by the treating physician based on the individual patient's response.*

### *Proposed dosing in EU*

The proposed dosing schedule submitted to the EU was originally for "*one injection per month for six consecutive doses, followed by one injection every two months*." In response to EU advice, the proposed dosage was amended to:

- *After the initial injection, treatment is given monthly until visual and anatomic outcomes are stable for three monthly assessments. Treatment may then be continued with extended scheduled treatment intervals in patients experiencing stable or improving visual and anatomic outcomes.*
- *The interval between two doses should not be shorter than two months.*
- *If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended.*
- *Usually, monitoring should be done at the injection visits.*

This was considered at the 25-26 July Committee for Medicinal Products for Human Use (CHMP) meeting (minutes were not yet available at the time of this Overview).

### Conclusions about dosage recommendations

The two pivotal trials (COPERNICUS and GALILEO) show that aflibercept is of benefit for patients with macular oedema following CRVO. Most of the benefit observed after six (6) 1 monthly injections was seen after three (3) 1 monthly injections (Table 21).

The sponsor has provided letters from two ophthalmologists. Their clinical experience indicates that treatment needs to be tailored to individual patients. It is likely that ophthalmologists will tailor their approach to treatment of CRVO in a similar way to their approach to AMD (Table 22, below, compares the dosage recommendations for the two conditions). A minor caveat is that the evidence base for AMD is larger than for CRVO and there is some evidence for AMD that 2 monthly injections are as beneficial as 1 monthly injections.

Pending advice from the Advisory Committee on prescription Medicines (ACPM), the Delegate's preference was for succinct dosage recommendations along the lines of:

> *initiation with three (3) 1-monthly injections, followed by extend-and-treat, based on individual patient response.*

The sponsor's proposal, which is similar to the proposal before the EU, was also considered acceptable (although more verbose).

**Table 22: Dosage recommendations: neovasular age-related macular degeneration versus macular oedema following CRVO**

| | Neovascular age-related macular degeneration | Macular oedema following CRVO |
|---|---|---|
| USA | 2mg (0.05 mL) monthly for the first 3 months, followed by 2 mg every 2 months. Although Eylea may be dosed as frequently as monthly additional efficacy was not demonstrated for monthly versus 2-monthly injections | 2 mg monthly |
| EU | The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres.<br>Eylea treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.<br>After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections. | **Proposed**<br>After the initial injection, treatment is given monthly until visual and anatomic outcomes are stable for 3 monthly assessments. Treatment may then be continued with extended, scheduled treatment intervals in patients experiencing stable or improving visual and anatomic outcomes.<br>The interval should not be shorter than one month.<br>If there is no improvement in visual and anatomic outcomes over the course of the first 3 injections, continued treatment is not recommended.<br>Usually monitoring should be done at injection visits. |

| | Neovascular age-related macular degeneration | Macular oedema following CRVO |
|---|---|---|
| AUS | One injection per month for 3 consecutive months, followed by one injection every 2 months. | **Proposed**<br>Initiated with one injection every month for 6 months.<br>After the first 3 injections, consideration may be given to continue treatment monthly or with an extended interval based on visual and anatomic outcomes.<br>The interval between 2 doses should not be shorter than one month.<br>If visual acuity or anatomic outcomes indicate no benefit over the course of 3 injections, continued treatment is not recommended.<br>Monitoring should be done at the injection visits. During treatment extension through to completion of therapy, the monitoring schedule is determined by the treating physician based on individual patient response. |

**Minor question for ACPM**

The RMP evaluator has recommended a change in the existing PI from:

"*the treatment should only be delivered by specialist physicians;*

to

*"the treatment should only be delivered by specialist ophthalmologists"*.

Does the ACPM have any comments on this suggested change?

**Conditions of registration**: The following are proposed as conditions of registration:

- Implement EU RMP, Version 8.0 (dated 30 October 2012) with Australian Specific Annex to the EU RMP Version 8.0, Version 1.0 (dated November 2012) and any future updates.
- Any studies that identify safety concerns or provide updated safety information must be submitted to the TGA as soon as possible after completion for evaluation.

**Questions for sponsor**

The sponsor has responded to Recommendation 5 in the second round RMP evaluation report regarding labelling and the possibility medication errors. The OPR evaluator has some residual concerns. Does the sponsor want to respond to these residual concerns?

***ACPM advice sought***

The committee was requested to provide advice on the following specific issue:

- Recommended dosing schedule for inclusion in the PI.

The committee was (also) requested to provide advice on any other issues that may be relevant to a decision on whether or not to approve this application.

## Delegate's recommendation

The Delegate had no reason to say, at this time, that the application for extension of indication for Eylea should not be approved for registration.

## Response from sponsor

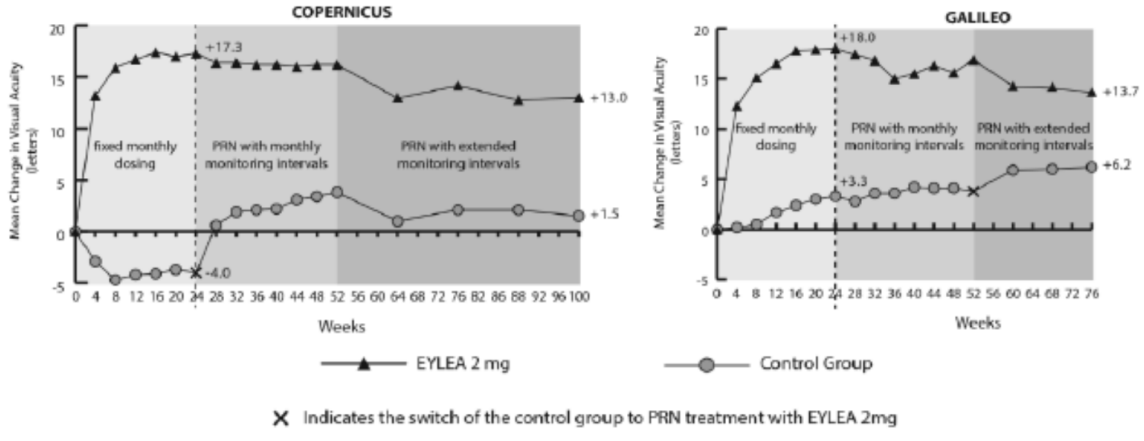
### *Justification for proposed dosage recommendation*

Central retinal vein occlusion (CRVO) is a progressive disease which could lead to vision loss. The principal cause of vision loss in CRVO is macular oedema. The consequence of chronic macular oedema may lead to permanent macular damage as well as other complications such as neovascularisation, vitreous haemorrhage and neovascular glaucoma. The clinical course of macular oedema following CRVO is variable and visual prognosis is poor. In Australia, therapeutic agents approved for the treatment of CRVO is limited. Eylea (aflibercept, also known as VEGF Trap-Eye) represents a clinically meaningful treatment option which provides sustained treatment efficacy in improving visual outcomes in patients with macular oedema secondary to CRVO.

### *Overview of the CRVO clinical program for Eylea*

The CRVO program comprised two pivotal studies of comparable design: GALILEO and COPERNICUS. Treatment was initiated with monthly injections in both trials. After Week 24, the treatment interval was extended with a fixed schedule of visit. The need for an injection or the possibility to defer the injection to the next visit was determined according to pre specified retreatment criteria based on visual and anatomic outcomes. As acknowledged by the Delegate "*there is no concerns about the efficacy and safety of aflibercept*" (VEGF Trap-Eye) as demonstrated in the two pivotal studies. Both pivotal studies indicated a robust superiority of Eylea over sham control. In particular, both studies successfully met its primary efficacy endpoint in demonstrating a statistically greater proportion of patients gained ≥ 15 ETDRS letters with Eylea treatment compared to sham at Week 24. Eylea led to statistically significant improvements in mean change in visual acuity as well as improvement in mean change in central retinal thickness from baseline (key secondary endpoints) compared to sham at Week 24. Overall, maximum efficacy in visual gains was achieved with Eylea early on, as early as after the first three injections. The superiority of Eylea over sham was maintained when the treatment interval was extended. Clinically meaningful vision gains as assessed by mean change in best corrected visual acuity (BCVA) from baseline was demonstrated by Eylea throughout the course of the study duration up to week 76/100. See Table 20 above and Figure 6 below.

**Figure 6: Mean change from baseline to Week 52 and Week/76/100 in visual acuity by treatment group for the COPERNICUS and GALILEO studies.**



Based on the protocol design, six doses were given consecutively at monthly interval for Week 0 to 24 in both pivotal studies. Both studies have shown that Eylea resulted in rapid and sustainable gains in visual acuity. Stability in visual gains was reached in the majority of patients after the first 3 injections. Comparison of the efficacy outcomes at Week 12 versus Week 24 (Table 21 above) and Kaplan Meier analysis, respectively, shows that most gains observed at Week 24 were already gained by Week 12. Most patients who gained ≥ 15 letters have achieved a sustained gain after the first three monthly injections.

***Proposed dosing schedule for on-going therapy***

The complete data from GALILEO and COPERNICUS through to 76/100 weeks have shown a successful extension of the treatment interval after the initial monthly injections. Sustained superiority in efficacy gains was observed with Eylea over sham throughout the course of the both studies. Clinically meaningful vision gains was maintained through to the end of study after the patients were switched to a "less frequent" dosing schedule from Week 24 onwards, see Figure 6. In both studies, the dosing experience from Week 24 onwards shows a variation in the number of active injections required during the on-going treatment phase (GALILEO: range of 0 to 9, mean = 3.7 ± 2.6 active injections during the 12 month period from Week 24 to 76; COPERNICUS: range of 0 to 15; mean = 6.0 ± 3.4 active injections during the 18 month period from Week 24 to 100). The sponsor proposes the following for inclusion in the PI to guide the extension of treatment interval for on-going therapy:

> *"… After the first three monthly injections, the treatment interval may be extended based on visual and anatomic outcomes. The interval between doses should not be shorter than one month…."*

The sponsor considered the above proposal appropriate as it provides clear and succinct guidance to physician based on the individual patient's visual and anatomic outcomes.

***Execution of the proposed "treat-and-extend" dosing schedule in clinical practice***

This proposed "treat-and-extend" dosing approach is well recognised in both literature and clinical practice in optimising on-going management of ocular diseases in clinical practice. The fundamental principle of the proposed "treat-and-extend" is that treatment would be given at each visit, and physicians would then adjust the timing of next visit based on the patient's visual and anatomic outcomes. The visit schedule is variable and the extension of treatment interval can be individualised to tailor to the patient's clinical need. Under the proposed "treat-and-extend" approach, patients will be monitored for visual and anatomic outcomes at each injection visit. Extension of the treatment interval would be carried out gradually in small increments of typically 1 to 2 weeks as long as the patient's visual and anatomic outcomes remain stable. Thereby at each visit, the subsequent treatment and monitoring interval for the individual patient is determined by the physician in an iterative process which aims to optimise disease control. Since monitoring is conducted in parallel with the injections at each visit, there is no need for monitoring in between for the patients. The sponsor thereby proposed the following for inclusion in the PI to provide guidance on monitoring under the proposed "treat-and-extend" dosing regimen:

> *"… Monitoring should be done at the injection visits. During treatment interval extension, the monitoring schedule should be determined by the treating physician based on the individual patient's response."*

On the whole, the sponsor considered the overall proposed posology wording an appropriate recommendation in clinical practice and also well aligned with the study design of COPERNICUS and GALILEO, whereby after a period of initial monthly injections the treatment interval was extended based on visual and anatomic outcomes. This proposed approach is also supported by the clinical experts in retinal ophthalmology as

noted in their respective statements submitted by the sponsor and acknowledged by the Delegate.

### *Benefit-risk balance*

Both Phase III pivotal studies, GALILEO and COPERNICUS, have successfully demonstrated the benefits of Eylea in the treatment of visual impairment due to macular oedema secondary to CRVO. Both studies indicated a robust superiority of Eylea over sham control with clinically meaningful visual gains observed throughout the entire study duration. Maximal improvement in visual acuity was achieved with Eylea after first three monthly injections, with subsequent stabilisation of the effect on visual acuity following monthly injections until Week 24. The visual improvements were successfully maintained thereafter through to Week 76/100 with an extension of the treatment interval. Eylea was well tolerated and a favourable safety profile was observed both during the treatment initiation with monthly injections as well as during the subsequent phase with extended treatment interval. The benefit-risk balance is assessed to be positive throughout. The amended posology wording proposed herein for ACPM's consideration was considered closely aligned with the study design and supported by the data from the pivotal studies. Thus, representing an appropriate translation of the studied doses into everyday clinical practice. Furthermore, it enables the physicians to tailor the treatment and monitoring interval to the individual patient to optimise disease control. The study results and the proposed posology are therefore assessed to have a positive benefits-risk balance overall.

### *Conclusion*

CRVO is a potentially blinding disease. The compelling results from both GALILEO and COPERNICUS clearly demonstrate the benefits of Eylea in the treatment of visual impairment due to macular oedema secondary to CRVO. Based on the available data and taking into account the severity and the burden of untreated CRVO, the sponsor concluded that the proposed dosing recommendation herein support the registration for Eylea for the requested indication and accommodates the treatment needs for Australian patients.

## Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications for a currently registered product. The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Eylea solution for injection containing 40 mg/mL of aflibercept (rch) to have an overall positive benefit–risk profile for the amended indication**:**

> *Visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) in adults.*

The committee was requested to provide advice on the following specific issue:

### *Recommended dosing schedule for inclusion in the PI*

The ACPM noted that the term "physician" could be misunderstood in the Australian context and advised that the dosage regimen for this indication should include statements to the effect that:

- *Eylea is for intravitreal injection only.*
- *It must only be administered by a qualified ophthalmologist experienced in administering intravitreal injections.*

- *Eylea treatment is initiated with one intravitreal injection per month for three months.*
- *After the first three injections, at no shorter than monthly intervals, the treatment interval may be extended, based on visual and anatomic outcomes.*
- *Monitoring of intra-ocular pressure post injection is critical and should be done at the injection visits. During treatment interval extension, the monitoring schedule should be determined by the treating ophthalmologist based on the individual patient's response.*

***Proposed conditions of registration***

The ACPM agreed with the Delegate on the proposed as conditions of registration:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- Any studies that identify safety concerns or provide updated safety information must be submitted to the TGA as soon as possible after completion for evaluation.

***Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments***

- As above, for recommended dosing schedule for inclusion in PI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Eylea (aflibercept) 40 mg/mL solution for intravitreal injection vial with needle and 40 mg/mL solution for intravitreal injection pre-filled syringe, indicated for:

> *Eylea (aflibercept) is indicated in adults for the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO).*

### Specific conditions applying to these therapeutic goods

1. The Eylea [aflibercept (rch)] EU Risk Management Plan (RMP) Version 8.0 dated 30 October 2012 with Australian Specific Annex to the EU-RMP Version 8.0, Version 1.0 (dated November 2012), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance in dudes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module Vll-Periodic Safety Update Report, Part Vll. B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

   Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be

submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

# Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

# Attachment 2. Extract from the Clinical Evaluation Report

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