Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Aflibercept (rch)

Proprietary Product Name: Eylea

Sponsor: Bayer Australia Ltd

11 February 2013

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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
2Q4	2mg (of VTE) administered every 4 weeks
2Q8	2 mg (of VTE) administered every 8 weeks
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AMD	Neovascular (wet) age-related macular degeneration
APTC	Antiplatelets Trialist's Collaboration
ATE	Arterial thromboembolic events
BCVA	Best corrected visual acuity
BP	Blood pressure
BRVO	Branch retinal vein occlusion
CFT	Central foveal thickness
CMH	Cochran-Mantel-Haenszel
CNV	Choroidal neovascularisation
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
ECG	Electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study

Abbreviation	Meaning
FA	Fluorescein angiography
FAS	Full analysis set
FDA	Food and Drug Administration
IOP	Intraocular pressure
IVT	Intravitreal
LOCF	Last observation carried forward
LSM	Least squares mean
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
PK	Pharmacokinetics
PlGF	Placental growth factor
PPS	Per protocol set
PRN	As needed
PRP	Panretinal photocoagulation
PT	Preferred term
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAF	Safety Analysis Set
TEAE	Treatment-emergent adverse event
TEAEI	Treatment-emergent adverse event of interest

Abbreviation	Meaning
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
VTE	VEGF Trap-Eye (Eylea)

1. Clinical rationale

The rationale for aflibercept for the treatment of Central retinal vein occlusion (CRVO) is based on the central role vascular endothelial growth factor (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 infarcts). 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, central retinal vein occlusion (CRVO) and branch retinal vein occlusion (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.[1] BRVO has been reported with a prevalence of about 3 times that of CRVO[2], and it has been estimated that CRVO affects approximately 2.5 million people worldwide.[3]

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.2 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.[4] Risk factors for CRVO, reported by the Eye Disease Case-Control Study Group, include hypertension, diabetes

[1] Wong TY and Scott IU. Retinal-vein occlusion. N Engl J Med. 2010; 363:2135-44.
[2] 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
[3] Laouri M, Chen E, Looman M, Gallagher M. The burden of disease of retinal vein occlusion: review of the literature. Eye. 2011, 1–8.
[4] 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.

mellitus, higher cardiovascular risk profile, and less physical activity.[5] Other possible risk factors predisposing to CRVO include age greater than 65 years[6], glaucoma or elevated intraocular pressure1,[6] renal disease[1], dyslipidemia[1], coagulopathy[6,7] and smoking[1]. Inflammatory disease within the eye may also contribute to pathogenesis.[1]

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 ischaemic and non ischaemic, CRVO baseline Visual acuity (VA) is generally poor (20/40) and in most patients it decreases over time.[8] The degree of retinal ischaemia is one of the major determinants of outcome in CRVO.[7] The principal causes of visual morbidity and complications of CRVO are macular oedema, vitreous haemorrhage, neovascularisation and neovascular glaucoma.[8] Macular oedema, with or without macular non-perfusion, is the most frequent cause of vision loss in patients with RVO[1] and is present to some degree in nearly all cases of CRVO.[7] There is a correlation between the severity of ischaemia and the risk of developing neovascularisation[9] 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 1 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.7 This treatment 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.[1] 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]

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 2 pivotal efficacy/safety studies: GALILEO Week 24, 52, and 76 clinical study reports; COPERNICUS Week 24, 52, and 100 clinical study reports.

[5] 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.
[6] Channa R, Smith M, Campochiaro PA. Treatment of macular edema due to retinal vein occlusions. Clinical Ophthalmology. 2011;5:705–713.
[7] London NJS, Brown G. Update and review of central retinal vein occlusion. Curr Opin Ophthalmol. 2011; 22:159–165.
[8] 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.
[9] 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.

- Integrated Analysis - Statistical Analysis Plans (6 months and 1 years 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 AE Tables and Figures; COPERNICUS 0819 Tables and Figures.
- References

2.2. 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.

2.3. 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).

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

PK data were submitted for subjects with CRVO from the Phase III study GALILEO. In addition, the Summary of Clinical Pharmacology included a *post-hoc* comparison of PK data in subjects with CRVO and subjects with wet-AMD.

3.2. GALILEO – pharmacokinetics

3.2.1. Overview

The PK assessment in GALILEO was divided into two parts: a mandatory part with assessment of systemic trough concentrations and a PK sub-study. PK data were available from the VEGF Trap-Eye (VTE) group in which subjects were treated with VTE 2 mg every 4 weeks by intravitreal (IVT) injection (VTE2Q4) from Week 0 to Week 20 and then with VTE 2 mg on an as needed basis (PRN) from Week 24 through to Week 76. No PK samples were collected after Week 52.

Free VEGF Trap and bound VEGF Trap plasma concentrations were measured using validated enzyme-linked immunosorbent assay (ELISA) methods. The assay for bound VEGF Trap was calibrated using VEGF:VEGF Trap complex standards. The results for bound VEGF Trap were reported as weight per volume (mg/L) of the complex (VEGF:VEGF Trap). One (1) ng of the VEGF:VEGF complex equals 0.717 ng VEGF Trap and 0.283 ng VEGF. Consequently, the concentration of the complex was multiplied by 0.717 to give an adjusted bound VEGF Trap concentration. The lower limit of quantitation (LLOQ) for the free and adjusted bound assays was 0.0156 mg/L and 0.0315 mg/L, respectively.

3.2.2. Mandatory PK assessment of trough concentrations

Mandatory PK assessment (sparse sampling schedule) of systemic trough concentrations of free and bound VEGF Trap were calculated from samples collected from all subjects in the per protocol set (PPS) Weeks 0 (baseline), 12, 24, 36 and 52.

Free VEGF Trap trough plasma concentrations at Weeks 12, 24, 36 and 52 were below the LLOQ for the assay for all subjects. Therefore, a planned exploratory sub-group analysis investigating the effects of possible covariates on the PKs of free VEGF Trap could not be undertaken.

Adjusted bound VEGF Trap mean (SD) trough plasma concentrations were 0.70 (6.37) µg/L at Week 0 (baseline/pre-dose) and 102 (48.7) µg/mL at Week 12. For the first time point (Week 0), one individual plasma sample from one subject had an adjusted bound VEGF Trap concentration above the LLOQ. This value was implausible as it was measured prior to the first injection of VTE. After Week 12, adjusted bound VEGF Trap mean (standard deviation (SD)) trough plasma concentrations increased only slightly to Week 24 (118 [71.2] µg/L) after which mean (SD) concentrations decreased to Week 36 (49.6 [53.6] µg/L) and Week 52 (69.8 [62.0] µg/L). The results are summarised below in Table 1.

Table 1: Concentration-time data for adjusted bound VEGF trap (µg/L); mandatory PK assessment of trough concentrations.

Time	N Total	N ≥ LLOQ	Arithm. Mean ± SD	Range
Week 0, pre-dose	82[a]	1[b]	0.70 ± 6.37	0 – 57.7
Week 12, pre-dose	84	82	102 ± 48.7	0 – 220
Week 24, pre-dose	16	16	118 ± 71.2	33.4 – 312
Week 36, pre-dose	38	22	49.6 ± 53.6	0 – 159
Week 52, pre-dose	28	20	69.8 ± 62.0	0 – 199

a: [information redacted] was previously included in this group in error. Blood samples for this subject were not collected at Visit 1 (that is, Week 0, pre-dose) as scheduled but were taken 4 weeks later at Visit 3. However, as Visit 3 was not a planned sampling time in the mandatory PK assessment, results from this time point (Visit 3) are not included in the assessment.
b: For the first time point (Week 0, pre-dose), one individual plasma sample [information redacted] had an adjusted bound VEGF Trap concentration above the LLOQ. This value for adjusted bound VEGF Trap concentrations is implausible as it was measured prior to the first injection of VEGF Trap-Eye. Therefore, results from this time point are not considered further.

The results for the **adjusted bound VEGF Trap** exploratory sub-group analysis of trough concentrations in the PPS at Weeks 12, 24, 36, and 52 for age, sex, body mass index (BMI), renal function, hepatic impairment, and geographic region were summarised in a table. The analysis is considered to be exploratory because of the small numbers of subjects in some sub-groups and the relative imbalance in subject numbers between some sub-groups. The results are summarised below:

- Higher bound VEGF Trap trough plasma concentrations were observed in the 65 to < 75 years age group compared with the < 65 years age group at all time points. The number of subjects in the ≥ 75 year age group was too small to meaningfully compare the data in this age group with the two younger age groups.
- Adjusted bound VEGF Trap trough plasma concentration was higher in females than in males at all time points, although the ranges in both sexes were wide and overlapping. For both females and males, trough plasma concentrations at Weeks 36 and 52 tended to be lower than at Weeks 12 and 24.
- Adjusted bound VEGF Trap trough plasma concentrations at Weeks 12 and 24 were higher in subjects with mild renal impairment compared with subjects with normal renal function, while the difference between the two sub-groups at Weeks 36 and 52 were relatively small. The number of subjects with moderate or severe renal impairment was too small to meaningfully compare the PK data in these two sub-groups with the PK data from the normal renal function or mild renal impairment sub-groups.
- There was no clear trend in adjusted bound VEGF Trap trough plasma concentrations with increasing BMI. The number of subjects with hepatic impairment was too small to meaningfully compare adjusted VEGF Trap trough plasma concentrations in this sub-group

with subjects with no hepatic impairment. There was no consistent difference in adjusted bound VEGF trap trough plasma concentrations at Weeks 24, 36 and 52 among the three geographical regions (Asia/Pacific; Europe; Japan). In each of the three regions, trough plasma concentrations at Week 36 and/or Week 52 were lower than at Weeks 12 and 24.

3.2.3. Exploratory sub-group PK analysis

The purpose of the PK sub-study (planned to be undertaken in 24 subjects from selected sites) was to assess the area under the plasma concentration time curve (AUC), peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}) and time to last measurable concentration (T_{Last}) of both free and adjusted bound plasma VEGF Trap following first and repeated dosing. Blood samples were drawn pre-dose, and then post-dose at 4, 8, 24, 48 (2 days), 72 (3 days), 96 (4 days), 168 (7 days), 336 (14 days) and 672 hours (28 days), after single (Week 0) and repeat dosing (Weeks 20 and 24). Non-compartmental PK analysis was undertaken for subjects with plasma concentrations >LLOQ and no more than 2 subsequently missing concentrations.

3.2.3.1. Free VEGF Trap (aflibercept) PK parameters

Samples were taken pre-dose and at various times up to 672 hours (28 days) after VTE administration. Across all time points, individual plasma concentration values for free VEGF Trap were below the LLOQ in 54% of subjects at Week 0, 70% of subjects at Week 20 and 67% of subjects at Week 24. At Weeks 0, 20 and 24 there were 7, 3 and 1 subjects, respectively, with evaluable PK data. In 50% of subjects, plasma concentrations declined to non detectable levels within 4 days after VTE administration. All subjects had free VTE plasma concentrations below 81 µg/L at all time points (LLOQ = 15.6 µg/L). Free VTE plasma concentrations declined to non-quantifiable levels in almost all subjects by 96 hours (4 days) post-injection. There was no evidence of accumulation of aflibercept following multiple dosing based on free aflibercept C_{max} and $AUC_{0\text{-}Last}$ values. The results for C_{max}, $AUC_{0\text{-}Last}$, T_{max} and T_{Last} are summarised below in Table 2.

Table 2: Free VEGF Trap pharmacokinetic parameters; PPS.

Para-meter		After 1st injection Week 0 (n=7)		After 6th monthly injection Week 20 (n=3)		After 7th monthly injection Week 24 (n=1)	
C_{max}	µg/L CV-G %[a]	45.6	(42.5%)	38.7	(71.0%)	23.6	(NC)
AUC (0-Last)	µg.h/L CV-G %)[a]	2847	(54.3%)	1440	(91.4%)	1762	(NC)
T_{max}	h range[b]	22.7	(7.9, 73.1)	8.0	(8, 95.2)	22.2	(NC)
T_{Last}	h range[b]	96.3	(70.8, 167)	95.2	(22.6, 96.1)	94.8	(NC)

Values < LLOQ not included; NC = not calculated. a = Geometric mean (coefficient of variation of geometric mean). b = Median (range).

3.2.3.2. Adjusted bound VEGF Trap (aflibercept) PK parameters

Samples were taken pre-dose and at various times up to 672 hours (28 days) after VTE administration. Across all time points, individual plasma concentration values for adjusted bound VEGF Trap were above the LLOQ in approximately 50% of subjects at Week 0 and increased to 100% at Week 20. At Weeks 0, 20 and 24 there were 8, 4 and 1 subjects, respectively, with evaluable PK data. All subjects had adjusted bound VEGF Trap individual plasma concentrations lower than 315 µg/L at all time points (LLOQ = 31.5 µg/L). At about 4

weeks post-injection, plasma concentrations of adjusted bound VTE had declined to non-detectable levels. The results for C_{max}, $AUC_{0\text{-}Last}$, T_{max} and T_{Last} are summarised below in Table 3.

Table 3: Adjusted bound VEGF Trap pharmacokinetic parameters; PPS.

Para-meter		After 1st injection Week 0 (n=7)		After 6th monthly injection Week 20 (n=3)		After 7th monthly injection Week 24 (n=1)	
C_{max}	µg/L CV-G% [a]	83.2	(31.5%)	193	(41.4%)	191	NC
AUC (0-Last)	µgh/L CV-G % [a]	41246	(41.6%)	86583	(46.5%)	98550	NC
T_{max}	h range [b]	336	(168-337)	168	(166-336)	335	NC
T_{Last}	h range [b]	683	(574, 745)	552	(432-669)	599	NC

Values < LLOQ not included; NC = not calculated. a = Geometric mean (coefficient of variation of geometric mean). b = Median (range).

3.2.4. Comparison of PK parameters – CRVO and wet-AMD

The sponsor's Summary of Clinical Pharmacology included a post hoc comparison of the systemic PKs of free and adjusted bound VEGF Trap in subjects with macular oedema due to CRVO and with wet-AMD. The systemic PKs of free and adjusted bound VEGF Trap has been described in the previous Eylea submission for the treatment of wet adult macular degeneration (wet-AMD). The broad demographic characteristics of the wet-AMD population were 44.5% male and 55.5% female, aged between 50 and 93 years (median: 75 years) with a mean body weight of 70.1±14.5 kg and mean body mass index (BMI) of 26.3±4.7 kg/m^2. In comparison, the broad demographic characteristics of the CRVO population were 56.3% male and 43.7% female, aged between 22 and 89 years (median: 63.9 years), with a mean body weight of 78.2±17.4 kg and a mean BMI of 27.5±5.1 kg/m^2.

In the PK comparison between subjects with CRVO (GALILEO) and subjects with wet-AMD (VGFT-OD-0702.PK), the arithmetic mean (coefficient of variation (CV)%) systemic C_{max} values for free VEGF Trap after single VTE 2 mg intravitreal (IVT) injections were low for both subjects with CRVO and wet-AMD (0.049 [39.3%] and 0.019 [118%] mg/L, respectively) and were only approximately 1 to 3 times the LLOQ (0.0156 mg/L). The arithmetic mean (CV%) systemic $AUC_{0\text{-}Last}$ values for free VEGF Trap after single doses were 0.133 mg.day/L (51.3%) in CRVO subjects and 0.119 mg.day/L (159%) in wet-AMD subjects. The CV% values for both the arithmetic mean systemic C_{max} and $AUC_{0\text{-}Last}$ values for free VEGF Trap in subjects with wet-AMD were very high (118% and 159%, respectively), indicating marked inter-subject variability in the 6 subjects from which the results were derived. The arithmetic mean adjusted bound VEGF Trap systemic C_{max} and $AUC_{0\text{-}Last}$ values were higher in subjects with wet-AMD than in subjects with CRVO. The arithmetic mean (CV%) adjusted bound VEGF Trap systemic C_{max} values were 0.086 (25.6%) and 0.186 (40.3%) ng/mL in the CRVO and wet-AMD subjects, respectively, and the corresponding $AUC_{0\text{-}Last}$ values were 1.82 (30.0%) and 4.43 (42.3%), respectively. Intersubject variability in the mean adjusted bound VEGF Trap systemic C_{max} and $AUC_{0\text{-}Last}$ in the 6 subjects in the wet-AMD group was moderate (CV% ~40%).

The systemic trough concentrations (C_{trough}) for adjusted bound VEGF Trap were compared in subjects with CRVO from GALILEO and subjects with wet-AMD from VIEW2. In subjects with CRVO, C_{trough} free VEGF Trap levels were below the LLOQ (0.0156 mg/ml) at Week 12 in all 84

subjects assessed. Similarly, in subjects with wet-AMD 130 (76.9%) of the 169 subjects assessed at Week 1 had Ctrough free VEGF Trap levels below the LLOQ (0.0156 mg/mL) and 162 (98.8%) of 164 subjects had levels below the LLOQ at Week 12. The arithmetic mean (SD) C_{trough} adjusted bound VEGF Trap at Week 12 was 0.102 (0.0487) mg/L (range: 0, 0.220) in subjects (n=84) with CRVO and 0.128 (0.0599) mg/L (range: 0, 0.388) in subjects (n=164) with wet-AMD. The C_{trough} range for adjusted bound VEGF Trap at Week 12 was broad in subjects with CRVO and with wet-AMD and the ranges were overlapping for the two subject groups. In the sub-group analysis of potential covariates affecting the systemic PKs of VTE, numerical differences between sub-groups at Week 12 in C_{trough} adjusted bound VEGF Trap in subjects with CRVO and subjects with wet-AMD were generally small, while the range of values in the sub-groups were broad and overlapping.

3.3. Evaluator's overall conclusions on pharmacokinetics

After single and multiple (every 4 weeks) 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 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, BMI, creatinine clearance, hepatic impairment and geographical region could not be conducted because all free VTE plasma trough concentrations were below the 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).

4. 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. These two parameters are considered to be directly relevant to the clinical efficacy and safety of VTE.

5. 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.

6. Clinical efficacy

6.1. 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 (VTE) 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.

6.2. Pivotal efficacy studies – GALILEO and COPERNICUS

6.2.1. Design, objectives, location and dates

COPERNICUS was conducted in approximately 70 centres with the majority of randomised subjects (n=189) being treated in centres in the USA (77.8%), followed by Canada (6.9%), Colombia (6.3%), Israel (5.3%) and India (3.7%). The submission included Week 24, Week 52 and Week 100 Clinical Study Reports (CSRs). For the Week 24 CSR (Amendment 1) the study period was 8 July 2009 to 21 October 2010, and the date of the report was 20 August 2010; for the Week 52 CSR (Amendment 1) the study period was 8 July 2009 to 27 April 2011, and the date of the report was 21 August 2012; and for the Week 100 CSR the study period was from 8 July 2009 to 4 April 2012, and the date of the report was 19 October 2012.

GALILEO was conducted in 63 study sites in 10 countries, Austria (3), France (5), Germany (21), Hungary (5), Italy (7), Latvia (2), Australia (6), Japan (6), Singapore (2), and South Korea (6). Of the 171 randomised subjects, the majority came from European centres (n=121; 70.8%) with the remainder (n=50; 29.2%) coming from Asian/Pacific centres. For the Week 24 CSR (Amendment 1) the study period was 28 October 2009 to 1 February 2011 and the report was dated 15 August 2012; for the Week 52 CSR (Amendment 1) the study period was 28 October

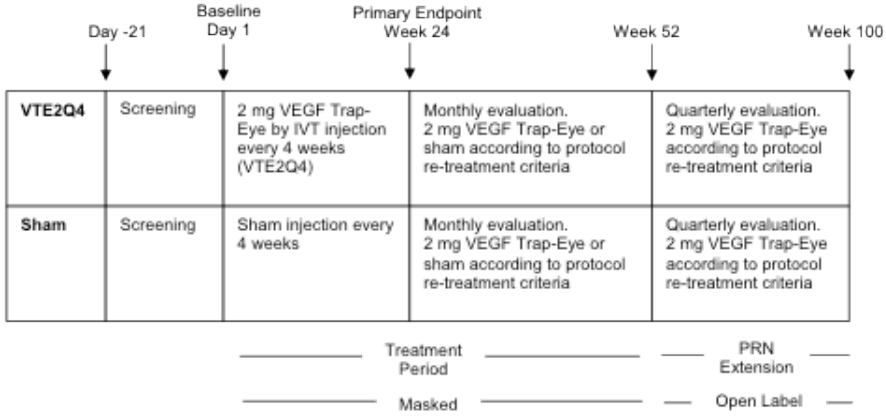
2009 to 22 July 2011, and the date of the report was 15 August 2012; and for the Week 76 CSR the study period was 28 October 2009 to 1 February 2012, and the date of the report was 8 October 2012.

The **primary objective** of both studies was to assess the efficacy of VTE IVT injections compared with standard of care (observation [sham injection]) on best corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol in subjects with macular oedema secondary to CRVO.

The **secondary objectives** of both studies were: (a) assessment of the safety and tolerability of VTE IVT injections compared with standard of care in subjects with macular oedema secondary to CRVO; and (b) assessment of the effects VTE IVT injections compared with standard of care on central retinal thickness (CRT) in subjects with macular oedema secondary to CRVO. In addition, the secondary objectives of GALILEO included assessment the PKs of free and bound VTE in a subset of subjects.

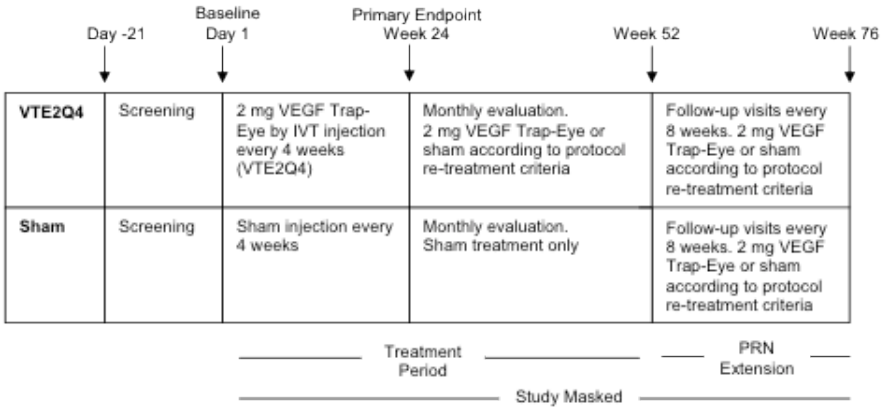
COPERNICUS planned to enrol approximately 165 subjects; 99 subjects in the VTE treatment group and 66 subjects in the sham treatment group. The study duration was 100 weeks (see Figure 1, below).

Figure 1: Copernicus – Study design.



GALILEO planned to enrol 165 subjects; 99 subjects in the VTE treatment group and 66 subjects in the sham treatment group. The study duration was 76 weeks (see Figure 2, below).

Figure 2: GALILEO – Study design.



In both studies, during screening (Day -21 to Day 1) subjects signed the consent form and underwent physical and ophthalmic examinations. In addition, laboratory samples were collected for baseline safety laboratory parameters, the National Eye Institute 25-Item Visual Functioning Questionnaire (NEI VFQ-25) quality of life (QOL) was administered, and medical/ophthalmic history and inclusion/exclusion criteria were reviewed.

In COPERNICUS, on Day 1 subjects were randomised to VTE2Q4 or sham (3:2 ratio) and treated through to and including Week 20, with the primary efficacy endpoint being assessed at Week 24, and treatment from Week 24 through to Week 100 being as outlined above in Figure 1. In the Week 52 to Week 100 period, subjects were evaluated quarterly and were treated with VTE if they met the pre-specified re treatment criteria. However, in this period VTE could be administered as frequently as every 4 weeks based on the investigator's opinion. Although Week 88 was the last mandatory study visit at which a PRN injection could be administered, the last possible PRN injection was at Week 96 for subjects receiving monthly injections.

In GALILEO, on completion of screening and confirmation of study eligibility subjects were randomly assigned to VTE2Q4 or sham (3:2 ratio) and treated from Day 1 through to an including Week 20, with the primary efficacy endpoint being assessed at Week 24 and treatment from Week 24 through to Week 76 as outlined above in Figure 2.

Comment: Both the pivotal Phase III studies were of similar design with the double-masked control treatment being sham. The studies appear to have been designed before the approval of Lucentis for the treatment of visual impairment due to macular oedema secondary to RVO. The sponsor states the sham control reflected the current standard of care at the inception of the clinical program, namely, observation until progression to anterior segment neovascularisation at which time treatment typically involved pan-retinal laser photocoagulation. In both studies, the primary efficacy analysis took place at Week 24 and the studies shared a similar design up to Week 24. However, after Week 24, the two studies had different designs (see above, Figures 1 and 2). In COPERNICUS, the sham+VTE PRN group from Week 24 to Week 100 included subjects who had been treated with sham or VTE, while in GALILEO the sham group from Week 24 to Week 52 included only subjects treated with sham and the sham+VTE PRN group from Week 52 to Week 76 included subjects who had been treated with sham or VTE.

6.2.2. Inclusion and exclusion criteria

The **key inclusion** criteria for **both studies** were:

- Adults at least 18 years of age.
- Centre-involved macular oedema secondary to CRVO with central retinal thickness (CRT) ≥250 μm on optical coherence tomography (OCT).
- Best corrected visual acuity (BCVA), using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, of 20/40 to 20/320 (73 to 24 letters) in the study eye.

The key exclusion criteria for both studies were:

- Only one functional eye, even if that eye was otherwise eligible for the study. Furthermore, subjects with only one eligible eye were not to have other ocular conditions with poorer prognosis in the fellow eye.
- Any prior or concomitant ocular (in the study eye) treatment or surgery for macular oedema secondary to CRVO, or systemic use of anti-VEGF products.
- Any prior or concomitant therapy with another investigational agent to treat macular oedema secondary to CRVO in the study eye.
- Any prior treatment with anti-VEGF agents in the study eye or previous administration of systemic anti-angiogenic medications.
- Bilateral manifestation of RVO.

There were minor differences between the studies in inclusion/exclusion criteria including:

- Subjects with a history of allergy to povidone iodine were excluded from the COPERNICUS study, but this was not listed as an exclusion criterion in GALILEO.

- Subjects with the prior use of anti-angiogenic drugs in the fellow eye were excluded from the COPERNICUS study, but this was not listed as an exclusion criterion in GALILEO.

The inclusion and exclusion criteria for COPERNICUS have been examined and are consistent with those for GALILEO, apart from the differences noted above.

Both studies also included criteria for withdrawal in the event of pre-specified events. These criteria have been examined and are considered to appropriate. Both studies also had satisfactory procedures in place to follow-up subjects who had prematurely discontinued.

6.2.3. Study treatments

In both studies, VTE was supplied by Regeneron and was administered by IVT injection using standard ophthalmic techniques. It was supplied in sealed, sterile 3 mL (40 mg/mL) single-use vials with a "withdrawable" volume of approximately 0.5 mL. Sham injections, using a syringe barrel without a needle, were performed with no active drug and without intraocular penetration. No dose escalations were allowed during the study.

The treatment regimens through to Week 100 for COPERNICUS and through to Week 76 for GALILEO are outlined above in Figures 1 and 2. The protocol specified re treatment was similar for the two studies. There were three re treatment criteria specified for deterioration and one re treatment criterion specified for improvement. The re treatment criteria were:

1. Re-treatment criteria for deterioration:
    a. greater than 50 μm increase in CRT compared to the lowest previous measurement as assessed by OCT;
    b. new or persistent cystic retinal changes or sub-retinal fluid as assessed by OCT or persistent diffuse oedema ≥ 250 μm in the central subfield as assessed by OCT;
    c. loss of 5 or more letters in BCVA compared to the best previous measurement in conjunction with any increase in CRT as assessed by OCT.
2. Re-treatment criterion for improvement.
    a. increase of 5 or more letters in BCVA compared with the most recent previous assessment.

In both studies, any other medication considered necessary for the subject's welfare, and not expected to interfere with the evaluation of the study drug, could be given at the discretion of the investigator. Subjects were not allowed to receive any medications (approved or investigational) for CRVO in the study eye other than the assigned study treatment until they had completed the end of study visit or early termination visit assessments. All subjects, regardless of treatment group, who progressed to anterior segment neovascularisation, neovascularisation of the disc (NVD), or clinically relevant neovascularisation elsewhere (NVE), could receive PRP at any time during the study. In COPERNICUS, subjects treated with PRP could remain in the study, while in GALILEO subjects treated with PRP were withdrawn from the study but could remain in the study for safety-follow up visits. The fellow eye was not considered an additional study eye and was not eligible to receive VTE. Subjects could not receive any investigational treatment for CRVO in the fellow eye. However, subjects who received treatment for the fellow eye were not required to be withdrawn from the study. Safety of the fellow eye was monitored and all adverse events (AEs) (ocular and systemic) were collected. Wet AMD in the fellow eye could be treated with ranibizumab.

6.2.4. Efficacy procedures and endpoints

6.2.4.1. Efficacy procedures

In both COPERNICUS and GALILEO, the following procedures were used to assess the efficacy endpoints:

1. Best-corrected visual acuity (BCVA) assessed using the ETDRS chart. Assessment was done at 4 metres. If the subject could correctly read only 19 or fewer letters at 4 meters assessment was repeated starting at 1 metre. Visual acuity (VA) examiners were certified to ensure consistent measurement of BCVA and all VA examiners remained masked to treatment allocation.
2. Optical coherence tomograph (OCT) was used to assess the retina of the study eye. All OCT images were captured using the Zeiss Stratus OCTTM software and transmitted to and read by a masked reader at the Independent Central Reading Center. OCT technicians were certified by the Independent Central Reading Center to ensure the consistency and quality of image acquisition, and all OCT technicians at the site were to remain masked to treatment assignment.
3. Fundus photography (FP) and fluorescein angiography (FA) were used to assess the retinal vasculature of the study eye. The FP and FA images were transmitted to the Independent Central Reading Center and read by masked readers ensure consistency and quality of image acquisition. All FP/FA technicians at the site were to remain masked to treatment assignment.
4. Vision-related quality of life (QOL) was assessed using the NEI VFQ-25 questionnaire in the interviewer-administered format and the local language and administered by masked study personnel.
5. In GALILEO, the overall state of health was assessed using the EQ-5D health questionnaire. The EQ-5D consists of five dimensions: Mobility, Self-care, Usual activities, Pain/discomfort, and Anxiety/depression. Each dimension has three levels, reflecting no health problems (Level 1), moderate health problems, and extreme health problems (Level 3). The questionnaire, in the local language, was administered, preferably before starting any other visit-related procedure, on Day 1, and Weeks 24, 52, and 76. In the event that a subject could not read the questionnaire due to visual impairment, the questionnaire was administered by masked study personnel.

6.2.4.2. Efficacy endpoints

The **primary efficacy endpoint** in COPERNICUS and GALILEO was:

- the proportion of subjects who gained 15 letters or more of BCVA (using the ETDRS protocol) at Week 24 from baseline.

The **secondary efficacy endpoints** in COPERNICUS and GALILEO were:

- change in BCVA from baseline to Week 24;
- change in CRT from baseline to Week 24;
- proportion of subjects progressing to any neovascularisation at Week 24;
- change in NEI VFQ-25 total score from baseline to Week 24.

GALILEO also included the change in the EQ-5D score from baseline to Week 24 a secondary efficacy endpoint.

The **tertiary efficacy endpoints** in COPERNICUS and GALILEO were: (1) changes in the NEI VFQ-25 subscales (distance activities, near activities, and vision dependency from Week 24); (2) proportion of subjects gaining ≥ 15 letters from baseline to Week 52; (3) change from baseline in BCVA score at Week 52; (4) change from baseline in CRT at Week 52; (5) proportion of subjects progressing to neovascularisation by Week 52; (6) change from baseline in the NEI VFQ-25 total score at Week 52; (7) changes in the NEI VFQ-25 subscales from baseline to Week 52. GALILEO also included the change in the EQ-5D score from baseline to Week 52, and time to first anterior segment neovascularisation, NVD or NVE as tertiary efficacy endpoints. In

COPERNICUS a set of tertiary efficacy endpoints were also assessed at Week 100 and additional (exploratory) efficacy endpoints were assessed at Week 76 in GALILEO.

Comment: The efficacy endpoints are all considered to be satisfactory. The ETDRS protocol used to assess BCVA is considered to be appropriate and has been used to assess changes in BCVA in other submissions relating to IVT injections to treat macular oedema secondary to RVO (Lucentis), AMD (Lucentis and Eylea) and DM (Lucentis). In addition, the proportion of subjects who gained at least 15 ETDRS in BCVA and the changes from baseline in mean BCVA have both been used to assess efficacy in pivotal Phase III studies of medicines to treat macular oedema irrespective of the underlying aetiology.

6.2.5. Randomisation and masking methods

6.2.5.1. Randomisation

In COPERNICUS, centralised randomisation stratified by geographic region (North America versus Rest of World) was undertaken by IRVS. In addition, subjects were stratified by baseline BCVA (> 20/200 [letters read 35 to 73] versus ≤ 20/200 [read 34 to 24]). It was anticipated that subjects with baseline BCVA ≤ 20/200 would more likely have ischaemic CRVO or be more likely to develop this condition.

In GALILEO, subjects were randomised based on stratification factors of geographic region (Europe versus Asia/Pacific) and baseline BCVA (≥ 35 letters versus ≤ 34 letters). The protocol specified that stratified randomisation based on geographic region (Europe versus Asia/Pacific) and baseline BCVA (> 20/200 versus ≤ 20/200). However, discrepancies were subsequently identified in the IVRS baseline BCVA strata for 30 subjects compared with actual baseline BCVA values. Consequently, the main analysis used the actual baseline BCVA values rather than the IVRS strata.

6.2.5.2. Masking

In COPERNICUS and GALILEO, IVT injections were performed by a physician unmasked to treatment assignment, with no role in the study beyond the administration of study drug and the conduct of post injection safety and ocular assessments. In both studies, a separate physician was assigned to the role of masked evaluator and this individual and all other study-site personnel remained masked to treatment assignment. In GALILEO, study treatment assignments remained masked to these individuals until database lock of the final 76-week data and authorisation of data release by responsible sponsor personnel. All subjects remained masked throughout the full conduct of the study. In COPERNICUS, masking was not mandated during year 2 (that is, Weeks 52 to 100) but the protocol "strongly recommended" that masked and unmasked roles be maintained until all enrolled subjects at a study site had completed Year 1 and entered the Weeks 52 to 100 PRN extension. In both COPERNICUS and GALILEO, unmasking of treatment assignment was permitted for medical emergencies.

6.2.6. Analysis populations

In both studies, the **full analysis set (FAS)** included all randomised subjects who received any study treatment, had a baseline ETDRS score and at least one post-baseline ETDRS score. The FAS was the primary efficacy analysis set and was analysed as randomised. The **per-protocol set (PPS)** included all subjects in the FAS who received at least 5 study treatments and did not have a major protocol violation (that is, a violation that may have affected the interpretation of the study results). The PPS was also used for the efficacy assessments and was analysed as treated. The **safety analysis set (SAF)** included all subjects who received any study treatment. The SAF was analysed as treated.

6.2.7. Sample size

In both COPERNICUS and GALILEO, subjects were randomly assigned in a 3:2 ratio (VTE:sham). A difference of 25% was anticipated between the two treatment groups in the proportion of

subjects gaining at least 15 letters, assuming that the proportion in the sham group was 15%.[10], and the proportion in the VTE group was 40%.9 To detect this difference, 90 subjects in the VTE group and 60 subjects in the sham group were needed to provide 90% power at a 5% significance level in a 2-sided Fisher's Exact test. To account for an approximate 10% dropout rate, 165 subjects (66 sham and 99 VTE) were to be randomised and treated. This sample size provided at least 90% power for the primary analysis using the Cochran-Mantel-Haenszel test stratified by region and baseline BCVA.

Comment: In COPERNICUS, 188 randomised subjects were treated with at least one dose of study drug from Week 0 to Week 24 (74 sham; 114 VTETQ4). In, GALILEO, 172 randomised subjects were treated with at least one dose of study drug from Week 0 to Week 24 (68 sham; 104 VTE2Q4). The randomised and treated subjects in both studies indicate that the power in both studies was at least 90%.

6.2.8. Statistical methods

6.2.8.1. Hypothesis

Both COPERNICUS and GALILEO examined the following hypotheses for the superiority testing of the primary efficacy variable: **H0 (null): pt = pc versus H1 (alternative): pt ≠ pc**; where pt is the proportion of subjects who gained at least 15 letters in BCVA compared with baseline at the Week 24 endpoint in the VTE group and pc is the proportion of subjects who gained at least 15 letters in BCVA compared with baseline at the Week 24 endpoint in the sham group.

6.2.8.2. Week-24 analyses

6.2.8.2.1. Analysis of the primary efficacy endpoint

In both COPERNICUS and GALILEO, the primary efficacy variable was the binary response (yes/no) of whether a subject gained at least 15 letters in BCVA on the ETDRS chart compared with baseline at Week 24. In COPERNICUS, subjects who discontinued prior to Week 24 and who had fewer than 5 study treatments were evaluated as non-responders in the primary analysis (otherwise missing values were imputed using last observation carried forward [LOCF]) and in GALILEO subjects who discontinued prior to Week 24 were evaluated as failures in the primary analysis. The primary efficacy analysis was conducted in the FAS, with analysis in the PPS being supportive.

In both studies, a two-sided Cochran-Mantel-Haenszel (CMH) tests at alpha level 5%, stratified by regions (North America versus Rest of World [COPERNICUS] or Europe versus Asia/Pacific [GALILEO]) and baseline BCVA (> 20/200 versus ≤ 20/200) was performed. In addition, a two-sided 95% CMH confidence interval adjusted for region and baseline BCVA was also calculated for the difference in proportions between the two treatment groups for subjects who gained at least 15 letters in BCVA. Sensitivity analyses using LOCF and observed value analyses were also conducted. Logistic regression was also performed as a secondary analysis of the primary efficacy variable at Week 24, with treatment group, region and baseline BCVA as fixed factors.

6.2.8.2.2. Analyses of the secondary efficacy endpoints

The analyses of the secondary efficacy endpoints were undertaken according to a pre-specified sequential testing strategy in order control for multiplicity and preserve an overall alpha of 0.05. In general, two-way analysis of co variance (ANCOVA) and/or analysis of variance (ANOVA) main effects models with treatment group, region, and baseline as fixed factors were used to analyse the endpoints. Sensitivity analyses for all secondary efficacy endpoints (except for progression to neovascularisation) were undertaken with missing values being replaced

[10] The Central Vein Occlusion Study Group. Evaluation of Grid Pattern Photocoagulation for Macular Edema in Central Vein Occlusion. *Ophthalmology*. 1995;102:1425-1433.

using the LOCF method. All secondary efficacy endpoint analyses were undertaken in the FAS with analyses in the PPS being supportive.

6.2.8.2.3. Sub-group analyses

Sub-group analyses were performed on the primary and secondary efficacy variables. Sub-group analyses for progression to neovascularisation were performed in COPERNICUS but were not interpretable because of the very small number of subjects (n=5 in the sham group and n=0 in the VTE2Q4 group) experiencing progression to neovascularisation.

6.2.8.3. Weeks 52 (both studies), 76 (GALILEO) and 100 (COPERNICUS) analyses

All efficacy outcomes assessed at Weeks 52, 76 and 100 were considered to be tertiary (exploratory) endpoints, with p-values being nominal and no adjustments being made for multiplicity of testing.

6.2.9. Participant flow

6.2.9.1. Disposition at Week 24

6.2.9.1.1. COPERNICUS

A total of 273 subjects were screened, 189 of whom were randomised (74, sham; 115, VTE2Q4). A total of 84 subjects were not randomised due to withdrawal of consent or inclusion/exclusion criteria violations.

Comment: The majority of all randomised subjects completed the first 24 weeks of the study (170 [89.9%]). However, the proportion of subjects completing the first 24 weeks was notably higher in the VTE2Q4 group compared with the sham group (95.7% versus 81.1%). A total of 19 (10.1%) subjects discontinued **the study** prior to Week 24, including 14 (18.9%) in the sham group and 5 (4.3%) in the VTE2Q4 group. The primary reasons for premature discontinuation of **the study** prior to Week 24 in the sham group were "treatment failure" (5.4%), and "adverse event" (4.1%). The primary reason for premature discontinuation of **the study** prior to Week 24 in the VTE2Q4 group was "withdrawal of consent" (2.6%). A total of 19 (10.1%) subjects discontinued **the study drug** prior to Week 24 (14 [18.9%] sham; 5 [4.3%] aflibercept). The reasons for premature discontinuation of the **study drug** in the sham group were identical to those leading to premature discontinuation of **the study**. However, while the total number of premature discontinuations due to **the study drug** prior to Week 24 in the VTE2Q4 group was identical to the number of premature discontinuations from **the study** prior to Week 24 there were minor differences in the reasons for discontinuation.

6.2.9.1.2. GALILEO

A total of 240 subjects were screened, 177 of whom were randomised (71, sham; 106, VTE2Q4). A total of 63 patients were not randomised, most of whom were considered to be screening failures (n=57). Of the 177 randomised patients, 172 received at least one treatment with sham (n=68) or VTE (n=104).

Comment: The majority of all randomised subjects completed the first 24 weeks of the study (122 [85.9%]). However, the proportion of subjects completing the first 24 weeks was notably higher in the VTE2Q4 group compared with the sham group (90.6% versus 78.9%, respectively). A total of 25 (14.1%) subjects discontinued the study prior to Week 24, including 15 (21.1%) in the sham group and 10 (9.4%) in the VTE2Q4 group. The primary reasons for premature discontinuation of the study prior to Week 24 in the sham group were "lack of efficacy" (7.0%), and "adverse event" (5.6%). The primary reason for premature discontinuation of the study prior to Week 24 in the VTE2Q4 group was "protocol violation" (4.7%). A total of 29 (16.4%) subjects discontinued the study drug prior to Week 24, including 18 (25.4%) in the sham group and 11 (10.4%) in the VTE2Q4 group. The proportion of subjects discontinuing the study drug prior to Week 24 due to "adverse events" was notably higher in the sham group than in the VTE2Q4 group (11.3% versus 1.9%, respectively). In addition, the

proportion of subjects discontinuing the study drug prior to Week 24 due to "lack of efficacy" was notably higher in the sham group than in the VTE2Q4 group (5.6% versus 0%, respectively).

6.2.9.2. Disposition - Week 52

6.2.9.2.1. COPERNICUS

Of the 189 randomised subjects (74, sham; 115, VTE2Q4), the majority (164 [86.8%]) completed the first 52 weeks of the study, including 57 (77.0%) in the sham+VTE PRN group and 107 (93.0%) in the VTE2Q4+PRN group. Overall, the proportion of subjects discontinuing the **study** or the **study drug** before Week 52 was similar (13.2% versus 13.8%, respectively). A total of 26 (13.8%) subjects prematurely discontinued the **study drug** before Week 52, including 18 (24.3%) in the sham+VTE PRN group and 8 (7.0%) in the VTE2Q4+PRN group. The primary reasons for discontinuing the **study dru**g prior to Week 52 in the sham+VTE PRN group were "adverse events" (5.4%) and "treatment failure" (5.4%), and the main reason in the VTE2Q4+PRN group was "withdrawal of consent" (4.3%). No subjects discontinued VTE2Q4+PRN prior to Week 52 due to "treatment failure".

6.2.9.2.2. GALILEO

Of the 177 randomised subjects (71, sham; 106, VTE2Q4), the majority (143 [80.8%]) completed the first 52 weeks of the study, including 52 [73.3%] in the sham group and 91 [85.8%] in the VTE2Q4+PRN group. Overall, the proportion of subjects discontinuing the **treatment** prior to Week 52 was greater than the proportion of subjects discontinuing the **study** (26.0% versus 19.2%). Subjects who discontinued treatment were allowed to remain in the study and continue protocol-specified evaluations. The proportion of subjects who discontinued **treatment** prior to Week 52 was 35.2% in the sham group and 19.8% in the VTE2Q4+PRN group. The most frequently reported primary reason for discontinuation of **treatment** prior to Week 52 was "adverse event" (VTE2Q4+PRN 5.7% versus sham 12.7%). No subjects in the VTE2Q4+PRN group discontinued study treatment due to "lack of efficacy" compared with 7% of subjects in the sham group.

6.2.9.3. Disposition beyond Week 52

6.2.9.3.1. COPERNICUS – Disposition at Week 100

The majority of subjects completed 100 weeks (152 [80.4%]), including 67.6% (n=50) in the sham+VTE PRN group, and 88.7% (n=102) in the VTE2Q4+PRN group. A total of 37 (19.6%) subjects discontinued **the study** prior to Week 100, including 24 (32.4%) in the sham+VTE PRN group and 13 (11.3%) in the VTE2Q4+PRN group. The primary reasons for discontinuation of **the study** prior to Week 100 in the sham+VTE PRN group were "lost to follow-up" (6.8%), "adverse event" (5.4%), "death" (5.4%), and "treatment failure" (5.4%), and in the VTE2Q4 group the main reason was "withdrawal of consent" (4.3%). The majority of subjects (151 [79.9%]) completed 100 weeks of treatment with the **study drug**, including 68.9% (n=51) in the sham+VTE PRN group and 87.0% (n=100) in the VTE2Q4+PRN group. The main reasons for discontinuation of the **study drug** before Week 100 in the sham+VTE PRN group were "adverse event" (5.4%), "death" (5.4%), "lost to follow-up" (5.4%) and "treatment failure" (5.4%), and in the VTE2Q4+PRN group the main reason was "adverse event" (5.2%).

6.2.9.3.2. GALILEO – Disposition at Week 76

The majority of subjects completed 76 weeks (142 [80.2%]), including 73.2% (n=52) in the sham+VTE PRN group and 84.9% (n=90) in the VTE2Q4+PRN group. A total of 35 (19.8%) subjects discontinued **the study** prior to Week 76, including 19 (26.8%) in the sham+VTE PRN group and 16 (15.1%) in the VTE2Q4+PRN group. Completion of the 76-week study was not necessarily associated with completion of study treatment during this period (that is, subjects who discontinued study treatment were allowed to remain in the study and continue to undergo the protocol-specified evaluations). The majority of subjects completed 68 weeks of

study treatment (137 [77.4%]), including 70.4% (n=50) in the sham+VTE PRN group and 82.1% (n=87). Discontinuation of **study treatment** prior to Week 76 occurred in a total of 40 (22.6%) subjects, including 21 (29.6%) in the sham+VTE PRN group and 19 (17.9%) in the VTE2Q4+PRN group. The most frequently reported primary reason for discontinuation of **study treatment** prior to Week 76 was "adverse event" (sham+VTE PRN 12.7% versus VTE2Q4+PRN 6.6%). No subjects in the VTE2Q4+PRN group discontinued **study treatment** for a lack of efficacy compared with 7% of subjects in the sham+VTE group. No subjects died during the 72-weeks study.

6.2.9.4. Major protocol violations/deviations

6.2.9.4.1. COPERNICUS

In the Week 24 analysis there were 6 (3.2%) subjects with major protocol deviations, including 3 (4.1%) subjects in the sham group and 3 (2.6%) subjects in the VTE2Q4 group. The major protocol deviations in the two treatment groups (sham versus VTE2Q4) were: inclusion/exclusion criteria error at study entry (2 [2.7%] versus 1 [0.9%]); treatment deviation (1 [1.4%] versus 1 [0.9%]); and procedure deviation (0 [0%] versus 1 [0.9%]). The 3 randomised subjects with "inclusion/exclusion criteria error at study entry" had been enrolled despite having bilateral RVO and without meeting the 3-month washout period for intraocular steroids. Overall, there were 150 (79.4%) subjects with minor protocol deviations in the study at Week 24.

In the Week 52 analysis, 1 additional subject in the VTE2Q4+PRN group had a major protocol deviation described as "excluded concomitant treatment" and 177 (93.7%) subjects had one or more minor protocol deviations. In the week-100 analysis, major protocol deviations from baseline to Week 100 were reported in 9 (4.8%) subjects, including 3 (4.1%) subjects in the sham+VTE PRN group and 6 (5.2%) subjects in the VTE2Q4+PRN group (see Table 4 below). From baseline through Week 100, a total of 183 (96.8%) subjects had one or more minor protocol deviations. Overall, 2 subjects were prematurely unmasked during the 100 weeks of the study; 1 unmasked during the first 24 weeks due to a serious adverse event (SAE) of central retinal artery occlusion; and 1 unmasked in the VTE2Q4+PRN group at day 342 due to an error in the injection procedure.

Table 4: COPERNICUS – Week 100 protocol deviations from baseline; all randomised patients.

	VEGF Trap-Eye		
	Sham+PRN (N=74)	2Q4+PRN (N=115)	Total (N=189)
Number of subjects with any protocol deviation	72 (97.3%)	111 (96.5%)	183 (96.8%)
Subjects with any minor protocol deviation	72 (97.3%)	111 (96.5%)	183 (96.8%)
Subjects with any major protocol deviation	3 (4.1%)	6 (5.2%)	9 (4.8%)
Type of major protocol deviation	3 (4.1%)	6 (5.2%)	9 (4.8%)
Inclusion/Exclusion Error at Study Entry	2 (2.7%)	1 (0.9%)	3 (1.6%)
Procedure Deviation	0	1 (0.9%)	1 (0.5%)
Treatment Deviation	1 (1.4%)	1 (0.9%)	2 (1.1%)
Withdrawal Criteria Present, But not Withdrawn	0	1 (0.9%)	1 (0.5%)
Excluded Concomitant Treatment	0	2 (1.7%)	2 (1.1%)
Other Protocol Deviation	0	1 (0.9%)	1 (0.5%)

6.2.9.4.2. GALILEO

In the week-24 analysis there were 25 (14.1%) subjects with a major protocol deviation, including 10 (14.1%) subjects in the sham group and 15 (14.2%) subjects in the VTE2Q4 group. The major protocol deviations in the two treatment groups (sham versus VTE2Q4) were: inclusion/exclusion error at study entry (6 [8.5%] versus 9 [8.5%]); excluded concomitant treatment (4 [5.6%] versus 6 [5.7%]); procedure deviation (0 [0%] versus 1 [0.9%]); and treatment deviation (0 [0%] versus 1 [0.9%]). Overall, there were 151 (85.3%) subjects with a least one protocol deviation, including 65 (91.5%) subjects in the sham group and 86 (81.1%) subjects in the VTE2Q4 group. Three (3) subjects in the VTE2Q4 group were found to have

BRVO after having received 2 to 3 injections and were discontinued from the study for a protocol violation.

In the Week 52 analysis there were 57 (32.2%) subjects with a major protocol deviation, including 45 (42.5%) subjects in the VTE2Q4+PRN group and 12 (16.9%) subjects in the sham group. The most notable difference between the two treatment groups was the higher proportion of subjects with major protocol deviations due to treatment deviations in the VTE2Q4 group compared with the sham group (32 [30.2%] versus 2 [2.8%]). In the Week 76 analysis there were 71 (40.1%) subjects with major protocol deviations including 50 (47.2%) subjects in the VTE2Q4+PRN group and 21 (29.6%) subjects in the sham+VTE PRN group. The major difference between the two treatment groups was the notably higher proportion of subjects with major protocol deviations due to treatment deviations in the VTE2Q4+PRN group compared with the sham+VTE PRN group (39[36.8%] versus 11 [15.5%]) (see Table 5, below). Three (3) subjects were prematurely unmasked during the 76 weeks of the study (2 between weeks 24 and 52, and 1 between weeks 52 and 76).

Table 5: GALILEO – Week-76 protocol deviations from baseline; all randomised subjects.

	Sham+VTE PRN N=71	VTE2Q4+PRN N=106	Total N=177
Number of minor protocol deviations	656	829	1485
Number of major protocol deviations	38	91	129
Subjects (%) with any protocol deviation	69 (97.2)	100 (94.3)	169 (95.5)
Subjects (%) with any major protocol deviation	21 (29.6)	50 (47.2)	71 (40.1)
Type of major protocol deviation; subjects (%)[a]			
Inclusion/exclusion error at study entry	7 (9.9)	10 (9.4)	17 (9.6)
Excluded concomitant treatment	4 (5.6)	6 (5.7)	10 (5.6)
Procedure deviation	0	1 (0.9)	1 (0.6)
Treatment deviation	11 (15.5)	39 (36.8)	50 (28.2)

a: a single subject may have had more than one major protocol deviation

6.2.9.5. Baseline data

6.2.9.5.1. COPERNICUS

Baseline demographics: In the FAS, demographics and baseline characteristics were generally well balanced between the two treatment groups. Just over half of the subjects were male (107/187; 57%) and the majority of the total population were white (147/187; 78.6%). The total population ranged in age from 22 to 89 years, with a mean (SD) of 66.3 (13.9) years. Baseline mean (SD) weight was 81.7 (19.6) kg, with an overall mean (SD) BMI of 28.7 (6.0) kg/m^2 and mean (SD) height was 168.5 (10.7) cm. Most subjects took medication prior to the study (180/187, 96.3%).

Baseline disease characteristics (study eye) In the FAS, baseline disease characteristics in the study eye were well balanced between the two treatment groups. In the majority of subjects (75.4%) baseline BCVA in the study eye was > 20/200 (letters ≥ 35). In most subjects (67.9%) the retinal status was considered to be perfused. In the total FAS (n=187), mean (SD) visual acuity using the ETDRS was 50.0 (14.1) letters (range: 20, 73 letters), retinal thickness was 665.8 (239.8) µm (range: 142, 1366 µm), intraocular pressure (IOP) was 15.1 (3.1) mmHg (range: 7, 22 mmHg), and time since CRVO diagnosis was 2.4 (2.8) months (range: 0, 18.2 months).

Baseline NEI VFQ scores: The NEI VFQ total score and subscores were similar for the two treatment groups as was the vision dependency score.

Vital signs: The mean baseline systolic and diastolic blood pressure, pulse rate and body temperature were all comparable between the two treatment groups and within normal ranges.

Baseline coagulation factors: The mean baseline coagulation factors (APPT, INR, PT) were comparable between the two treatment groups and within normal ranges.

Non-ocular and ocular medical/surgical history: In the safety analysis set (SAF), all subjects in both treatment groups had a history of at least one medical or surgical event at baseline. The most commonly reported medical or surgical history findings at baseline in subjects in the SAF (n=188) consisted of eye disorders (100%), vascular (75.0%), surgical and medical procedures (69.1%), and metabolism and nutrition disorders (55.9%). The disorders with a ≥ 5% difference between the two treatment groups (sham [n=74] versus VTE2Q4 [n=114]) and occurring in ≥ 10% of subjects in either treatment group were: vascular disorders (71.6% versus 77.2%); surgical and medical procedures (63.5% versus 72.8%); immune system disorders (21.6% versus 33.3%); cardiac disorders (31.3% versus 24.6%); respiratory, thoracic and mediastinal disorders (21.6% versus 28.9%); reproductive system and breast disorders (12.2% versus 25.4%); skin and subcutaneous tissue disorders (8.1% versus 14.0%).

Ocular (study eye) medical/surgical history: The most commonly reported history of ocular disorders in the study eye (SAF) occurring in ≥ 10% of subjects in at least one of the treatment groups in decreasing order of frequency in the sham group were (sham [n=74] versus VTE2Q4 [n=114]): retinal vein occlusion (100% versus 100%); macular oedema (91.9% versus 95.6%); cataract (41.9% versus 56.1%); nuclear cataract (23.0% versus 8.8%); retinal haemorrhage (24.3% versus 23.7%); cataract operation (21.8% versus 17.5%); glaucoma (16.2% versus 7.0%); retinal vascular disorder (12.2% versus 7.9%); vitreous detachment (13.5% versus 22.8%); papilloedema (10.8% versus 7.9%); and intraocular lens implant (6.8% versus 10.5%).

Ocular (fellow eye) medical/surgical history: The most commonly reported history of ocular disorders in the fellow eye (SAF) occurring in ≥ 10% of subjects in at least one of the treatment groups in decreasing order of frequency in the sham group were (sham [n=74] versus VTE2Q4 [n=114]): cataract (39.2% versus 55.3%); cataract nuclear (21.6% versus 7.9%); vitreous detachment (17.6% versus 20.2%); cataract operation (16.2% versus 19.3%); and intraocular lens implant (6.8% versus 11.4%).

Non-ocular medical/surgical history: In the total population (SAF), the most commonly reported history of non-ocular disorders occurring in ≥ 10% of subjects (n=188) in decreasing order of frequency were: hypertension (70.7%); hypercholesterolemia (27.7%); drug hypersensitivity (19.1%); gastroesophagael reflux disease (17.6%); depression (17.0%); hysterectomy (16.0%); hypothyroidism (14.4%); osteoarthritis (12.2%); hyperlipidaemia (12.2%); diabetes mellitus type 2 (11.2%); arthritis (10.6%); and seasonal allergy (10.1%).

Capillary perfusion status: In the FAS, baseline capillary perfusion status in subjects in the total population was: perfused (< 10 disc areas [DA] of capillary non-perfusion), n=127 (67.9%); non-perfused (≥ 10 DA of capillary non-perfusion), n=29 (15.5%); indeterminate, n=31 (16.6%); and missing, n=0 (0%). There were no noteworthy differences in baseline capillary status between the two treatment groups.

Prior medications (SAF): Overall, 97.3% (72/74) of subjects in the sham group had taken medications prior to VTE compared with 95.6% (109/114) of subjects in the VTE2Q4 group. The most commonly used prior therapies (≥ 40% in at least one of the treatment groups) in decreasing order of frequency in the sham group (versus VTE2Q4) were: ophthalmologicals (64.9% versus 60.5%); cardiac (51.4% versus 50.9%); stomatological preparations (45.9% versus 36.8%); serum lipid reducing agents (43.2% versus 46.5%); and agents acting on the renin-angiotensin system (33.8% versus 45.6%). Prior therapies taken in ≤ 40% of subjects in either treatment group, but with a ≥ 5% difference between the two treatment groups (sham versus VTEQ24) and occurring in ≥ 10% of subjects in at least one of the two treatment groups were: vitamins (36.5% versus 20.1%); calcium channel blockers (23.0% versus 17.5%); gastrointestinal (GIT) drugs for acid related disorders (27.0% versus 20.2%); drugs used in diabetes (17.6% versus 23.7%); analgesics (14.9% versus 20.2%); anti-inflammatory and anti-rheumatic products (13.5% versus 7.9%); antiepileptics (12.2% versus 3.5%); and psychoanalpetics (10.8% versus 20.2%).

Concomitant medications up to Week 24 (SAF): Overall, 100% of subjects in both treatment groups took concomitant medications up to Week 24. Concomitant medications taken by ≥ 40% of subjects in either treatment group (sham [n=74] versus VTE2Q4 [n=114]) in decreasing order of frequency in the sham group were: ophthalmologicals (100% versus 99.1%); antiseptics and disinfectants (93.2% versus 90.4%); systemic antibacterials (91.9% versus 98.2%); cardiac (90.5% versus 86.0%); stomatological preparations (50.0% versus 42.1%); serum lipid reducing agents (44.6% versus 48.2%); agents acting on the renin-angiotensin system (39.2% versus 48.2%); and beta-blocking agents (39.2% versus 40.4%).

6.2.9.5.2. GALILEO

Baseline demographics: In the FAS, demographic characteristics were well balanced between the two treatment groups. Slightly more than half of the subjects were male (95/171; 55.6%), and most of the total population were White (123/171; 71.9%). The total population ranged in age from 29 to 88 years, with a mean (SD) of 61.5 (12.9) years, mean (SD) weight of 74.6 (15.1) kg, mean (SD height of 168.1 (10.2) cm, and mean (SD) BMI of 26.3 (4.2) kg/m^2.

Baseline disease characteristics (study eye): In the FAS, baseline BCVA letter scores were well balanced between the two treatment groups, with the majority of subjects in the sham and VTE2Q4 groups having a BCVA of > 20/200 (≥ 35 letters) (82.4% versus 83.5%, respectively), and similar mean (SD) visual acuity (letters) (50.9 [14.4] versus 53.6 [15.8], respectively). There was an imbalance between the two treatment groups in baseline retinal perfusion status, with a higher proportion of subjects in the VTE2Q4 group considered to be perfused compared with the sham group (86.4% versus 79.4%, respectively). Baseline mean intra ocular pressure (IOP) was similar in the two treatment groups and within the normal range. Time since CRVO diagnosis was < 2 months in 51.5% of subjects in the sham group and 53.4% in the VTE2Q4 arm.

Baseline NEI VFQ and ED-50 scores: Baseline NEI VFQ-25 scores and sub-group scores in subjects in the FAS were similar for the two treatment groups, as was the baseline EQ-5D score.

Vital signs: Mean baseline systolic and diastolic blood pressure, pulse rate and body temperature were all comparable in the two treatment groups (SAF) and within normal ranges.

Non-ocular and ocular medical/surgical history: In the SAF, all subjects (n=172) in both treatment groups had a history of at least one medical or surgical condition/event at baseline. In the total population, the most commonly reported conditions were eye disorders (100%), vascular disorders (60.5%), surgical and medical procedures (51.2%) and metabolism and nutrition disorders (40.7%). The disorders with a ≥ 5% difference between the two treatment groups (sham [n=68] versus VTE2Q4 [n=104]) and occurring in ≥ 10% of subjects in either treatment group were: vascular disorders (66.2% versus 56.7%); cardiac disorders (32.4% versus 23.1%); nervous system disorders (25.0% versus 18.3%); infections and infestations (20.6% versus 7.7%); reproductive system and breast disorders (17.6% versus 6.7%); neoplasms benign, malignant and unspecified (7.4% versus 12.5%); hepatobiliary disorders (4.4% versus 10.6%); and congenital, familial and general disorders (4.4% versus 10.6%).

Ocular medical/surgical history (study eye): In the total SAF population (n=172), the most commonly reported conditions were retinal vein occlusion (98.8%) and macular oedema (61.0%). The conditions with a ≥ 5% difference between the two treatment groups (sham [n=68] versus VTE2Q4 [n=104]) and occurring in ≥ 10% of subjects in either treatment group were: macular oedema (67.6% versus 56.7%); retinal haemorrhage (39.7% versus 28.8%); and papilloedema (23.5% versus 17.3%).

Ocular medical/surgical history (fellow eye): In the total SAF population (n=172), 70.6% (48/68) of subjects in the sham group had a medical/surgical history of ocular conditions in the fellow eye compared with 61.5% (64/105) of subjects in the VTE2Q4 group (n=104). Conditions in the fellow eye occurring in ≥ 10% of subjects in either treatment group (sham versus VTE2Q4) were cataract (30.9% versus 33.7%), and cataract operation (10.3% versus 6.7%).

Prior medications: In the SAF population (n=172), 29.4% (20/68) of subjects in the sham group had taken at least one medication prior to the start of study drug treatment compared with 31.7% (33/104) in the VTE2Q4 group. Medications taken by ≥ 10% of subjects in either treatment group (sham versus VTE2Q4) were: ophthalmologicals (16.2% versus 16.3%); blood substitutes and perfusion solutions (13.2% versus 9.6%); and peripheral vasodilators (10.3% versus 14.4%). In general, the use of prior medications was similar between the two treatment groups.

New concomitant medication up to Week 24: In the SAF population (n=172), all subjects in the sham group (n=68) and the VTE2Q4 group (n=104) took at least one new concomitant medication up to Week 24. The new concomitant medications taken by ≥ 10% of subjects in both treatment groups (sham versus VTEQ4) were: ophthalmologicals (98.5% versus 99.0%); antibacterials for systemic use (76.5% versus 71.2%); throat preparations (75.0% versus 78.8%); antipuritics (66.2% versus 53.8%); stomatological preparations (63.2% versus 67.3%); gynaecological anti-infectives/disinfectants (57.4% versus 65.4%); antiseptics/disinfectants (55.9% versus 64.4%); medicated dressings (55.9% versus 64.4%); vasoprotectives (51.5% versus 44.2%); anaesthetics (48.5% versus 37.5%); otologicals (38.2% versus 36.5%); cardiac (32.4% versus 31.7%); analgesics (23.5% versus 17.3%); nasal preparations (23.5% versus 13.5%); ophthalmological/otological preparations (16.2% versus 14.4%); and antibiotics and chemotherapies for dermatological use (13.2% versus 11.5%).

6.3. Results for efficacy endpoints-Week-24

6.3.1. Primary efficacy endpoint analysis -Week-24

The proportion of subjects (FAS) gaining ≥ 15 letters in BCVA from baseline to Week 24 in both studies are summarised below in Table 6.

Table 6: COPERNICUS and GALILEO, results for the primary efficacy analysis of proportion of subjects gaining ≥ 15 letters in BCVA from baseline to Week 24; FAS.

	COPERNICUS [1]		GALILEO [2]	
	Sham (n=73)	VTE2Q4 (n=114	Sham (n=68)	VTE2Q4 (n=103)
Number (%) who gained ≥ 15 letters in BCVA	9 (12.3%)	64 (56.1%)	15 (22.1%)	62 (60.2%)
Difference [3] (%)	43.8%		38.1%	
CMH adjusted difference [3,4] (%) (95% CI)	44.8% (95% CI: 33.0, 56.6)		38.3% (95% CI: 24.4, 52.1)	
p-value [5]	p < 0.0001		P < 0.0001	

[1] COPERNICUS, subjects who discontinued before Week 24 with fewer than 5 treatments were considered to be non-responders, otherwise missing values were imputed using LOCF analysis.
[2] GALILEO, subjects who discontinued prior to Week 24 were considered to be treatment failures.
[3] Difference is VTE2Q4 minus sham.
[4] Point estimate and CI are calculated using CMH weights adjusted for region (North America versus Rest of World [COPERNICUS]; Europe versus Asia/Pacific [GALILEO]) and baseline BCVA category (> 20/200 versus ≤ 20/200 [both studies]).
[5] p-value is calculated using 2-sided CMH-test adjusted by region and baseline BCVA category.

In both COPERNICUS and GALILEO, the primary endpoint analysis in the PPS was consistent with the primary endpoint analysis in the FAS and supported the statistical and clinical superiority of VTE2Q4 compared with sham.

In COPERNICUS, the sensitivity analyses of the proportion of subjects who gained at least 15 letters in BCVA at Week 24 in the FAS and PPS using LOCF, observed values, and evaluating subjects with < 5 injections as failures were summarised in three tables. The results for the sensitivity analyses (FAS, PPS) were similar to the corresponding results in the primary analyses (FAS, PPS). In GALILEO, the sensitivity analyses of the proportion of subjects who gained at least 15 letters in BCVA at Week 24 in the FAS and PPS using LOCF, observed values, and evaluating subjects with < 5 injections as failures were summarised in a table. The results for the sensitivity analyses (FAS, PPS) were similar to the corresponding results in the primary analyses (FAS, PPS).

In COPERNICUS, the sub-group analyses of the primary efficacy endpoint in the FAS were generally consistent with the analysis in the overall population. However, 7 of the sub-groups are considered to have too few subjects to allow for any meaningful efficacy comparisons to be undertaken: race (any non-White sub-group); ethnicity (Hispanic or Latino): geographic region (Rest of World); renal function (moderate and severe impairment); history of hepatic impairment; baseline perfusion status (non-perfused); and baseline BCVA (≤ 20/200). The sub-group analyses were also undertaken in the PPS and these were consistent with those in the sub-group analyses undertaken in the FAS. In GALILEO, the sub-group analyses of the primary efficacy endpoint in the FAS were generally consistent with the analysis in the overall population. However, the sub-groups with too few subjects to allow meaningful efficacy analyses to be undertaken were similar to those in COPERNICUS. The sub-group analyses were also undertaken in the PPS and these were consistent with those in the sub-group analyses undertaken in the FAS.

In COPERNICUS, logistic regression modelling for the probability of gaining at least 15 letters in BCVA by Week 24 considering treatment, region, baseline BCVA and baseline perfusion status as fixed factors resulted in an OR estimate of 10.918 ([95% CI: 4.792, 24.872]; p< 0.0001) for VTE2Q4 versus sham. This OR indicates an approximate 11 fold increase in the odds of gaining at least 15 letters with VTE2Q4 compared with sham. The ORs for gaining at least 15 letters in BCVA by Week 24 showed no statistically significant difference in subjects stratified by region (Rest of World versus North America), baseline BCVA (> 20/200 versus ≤ 20/200), or perfusion status (perfused versus non-perfused). In GALILEO, logistic regression modelling in the FAS for the probability of gaining at least 15 letters in BCVA by Week 24 considering treatment, region, and baseline BCVA category as fixed factors resulted in an odds ratio (OR) estimate of 5.38 ([95% CI: 2.68, 10.80]; p < 0.0001) for VTE2Q4 versus sham. This OR indicates an approximate 5 fold increase in the odds of gaining at least 15 letters with VTE2Q4 compared with sham. The ORs for gaining at least 15 letters in BCVA by Week 24 showed no statistically significant difference in subjects stratified by region (Europe versus Asia/Pacific) or by baseline BCVA (> 20/200 versus ≤ 20/200). The analysis in the PPS was consistent with that in the FAS.

Comment: In both studies, the primary endpoint (FAS) of the proportion of subjects gaining ≥ 15 letters improvement in BCVA from baseline to Week 24 was statistically significantly greater in the VTE2Q4 group than in the sham group. In both studies, the difference between treatment groups was > 25% (i.e., the difference on which the sample size was based assuming a proportion of 15% in the sham group and 40% in the VTE2Q4 group). Consequently, it is considered that the difference between the two treatment groups in both studies is clinically as well as statistically significant. In both studies, the primary efficacy analysis in the FAS was supported by the analysis in the PPS and the sensitivity analyses. The sub-group analyses in the FAS and PP generally supported the primary efficacy analysis. In both studies, the OR for the probability of gaining at least 15 letters in BCVA derived from logistic regression modelling supported the superiority of VTE2Q4 compared with sham.

6.3.2. Secondary efficacy endpoints – Week 24

The results for the secondary endpoint analyses are summarised below in Table 7.

Table 7: CAPRICORN and GALILEO, overview of secondary efficacy endpoint results; order of testing in FAS.

Order	Secondary Endpoint	COPERNICUS		GALILEO	
1 [a]	1. Change in BCVA letter score from baseline to Week 24.	21.70 letters 95% CI: 17.36, 26.04	p < 0.0001 Favours VTE2Q4	14.7 letters 95% CI:10.8, 18.7	p < 0.0001 Favours VTE2Q4
2 [a]	2. Change in CRT from baseline to Week 24.	-311.9 µm 95% CI: -389.4, -234.4	p < 0.0001 Favours VTE2Q4	-239.43 µm 95% CI: -286.31, -192 .53	p < 0.0001 Favours VTE2Q4
3 [b]	3. Proportion of subjects progressing to neovascularisation by Week 24.	-6.8% 95% CI: -12.4, -1.2	p = 0.0059 Favours VTE2Q4	-1.5% 95% CI: -7.4, 4.4	p = 0.5947 Not significant
4 [a]	4. Change in NEI VFQ total score from baseline to Week 24.	6.62 95% CI: 2.61, 9.91	p = 0.0009 Favours VTE2Q4	4.2 95% CI: 1.7, 6.8	p = 0.0013 Nominal
5 [a]	5. Change in EQ-5D score from baseline to Week 24.	Not a secondary endpoint in COPERNICUS		0.044 95% CI: -0.002, 0.090	p = 0.0627 Nominal

[a]Difference and 95% CI for the treatment difference (VTE2Q4 minus sham) of the LS mean changes using an ANCOVA model with treatment group, region, and baseline BCVA as fixed factors. [b] CMH test controlling for region and baseline BCVA for each study.

Comment: In COPERNICUS, the hierarchical testing procedure demonstrated that VTE2Q4 was statistically significantly superior to sham for all four secondary efficacy endpoints. In GALILEO, the hierarchical testing procedure was stopped after the difference between VTE2Q4 and sham for the proportion of subjects progressing to neovascularisation by Week 24 was found to be not statistically significant (test #3). Consequently, the p values for the two subsequent secondary efficacy endpoint pair-wise comparisons (tests #4 and #5) were nominal rather than confirmatory.

6.3.3. Tertiary efficacy endpoints – Week-24

6.3.3.1.1. COPERNICUS

There was no statistical significant difference between the two treatment groups in LS mean change from baseline to Week-24 in the NEI VFQ-25 near activities score, with the LS mean change being 3.58 points in the sham group (n=73) and 9.89 points in the VTE2Q4 group (n=114) and the difference, adjusted by region and baseline BCVA, being 6.31 points (95% CI:. -0.55, 13.16); p=0.0711 (nominal). Near activities were defined as difficulty reading ordinary print in newspapers, performing work or hobbies requiring near vision or finding something on a crowded shelf.

There was a statistically significant greater improvement in distance activities measured by the NEI VFQ-25 distance activities score. The LS mean change from baseline was 8.06 points in the

VTE2Q4 group (n=73 and 1.57 points in the sham group (n=114) and the difference, adjusted by region and baseline BCVA, was 6.49 points (95% CI: 0.56, 12.42); p=0.0321 (nominal). Distance activities are defined as reading street signs or names on stores, and going down stairs, steps, or curbs.

There was no statistical significant difference between the two treatment groups in LS mean change from baseline to week-24 in the NEI VFQ-25 vision dependency score, with the LS mean change being 3.77 points in the sham group (n=73) and 9.62 points in the VTE2Q4 group (n=114) and the difference, adjusted by region and baseline BCVA, being 5.84 points (95% CI:. -0.76, 12.45); p=0.0825 (nominal). Vision dependency is defined as the need to stay at home, reliance on others, and need of help.

6.3.3.1.2. GALILEO

The LS mean change from baseline to Week 24 (FAS/LOCF) in the NEI VFQ-25 near activities subscore was 6.8 points in the VTE2Q4 group (n=96) and -1.8 points in the sham group (n=65), adjusted mean difference = 8.6 points (95% CI: 4.0, 13.2), p=0.0003 (nominal).

The LS mean change from baseline to Week 24 (FAS/LOCF) in the NEI VFQ-25 distance activities subscore was 2.7 points in the VTE2Q4 group (n=96) and -0.7 in the sham group (n=65) adjusted mean difference = 3.5 points (95% CI: -0.3, 7.2), p=0.0689 (nominal).

The LS mean change from baseline to Week 24 (FAS/LOCF) in the NEI VFQ-25 dependency subscore was 1.5 points in the VTE2Q4 group (n=96) and -0.7 in the sham group (n=65) adjusted mean difference = 2.1 points (95% CI: -1.6, 5.8), p=0.2552 (nominal).

6.3.4. Integrated analysis – Week-24

The submission included a non-confirmatory, post-hoc, 24 week integrated efficacy analysis of the primary, secondary and tertiary efficacy endpoints in the FAS using data from COPERNICUS and GALILEO. Overall, the results for the primary and secondary Week 24 efficacy endpoints in the non-confirmatory integrated efficacy analysis were consistent with the results from the analyses in COPERNICUS and GALILEO.

6.3.5. Results for tertiary efficacy endpoints at Week-52

Overall there were 3 tertiary efficacy endpoints in both studies comparing the proportion of subjects who gained 15 or more letters in the ETDRs letter score at 52 weeks in the two treatment groups, and 8 (COPERNICUS) and 9 (GALILEO) tertiary efficacy endpoints comparing a range of other efficacy endpoints between the two treatment groups. Nominal statistical significance favouring greater efficacy in the VTE2Q4+PRN group than in the sham group was observed in 8 of 11 endpoints in GALILEO, while in COPERNICUS nominal statistical significance favouring greater efficacy in the VTE2Q4+PRN group than in the sham+VTE PRN group was observed in 5 of 10 endpoints.

6.3.5.1. Results for tertiary (exploratory) efficacy endpoints at weeks 76 and 100

The nominal p-value was < 5% in favour of VTE2Q4+PRN for 2 of the 6 tertiary efficacy endpoint analyses at Week 100 (COPERNICUS). The nominal p-value was < 5% in favour of VTE2Q4+PRN for 4 of the 9 tertiary efficacy endpoints at Week 76 (GALILEO). The mean changes from baseline in BCVA by visit through to Week 76 (GALILEO) and Week 100 (COPERNICUS) in the FAS (LOCF) were provided.

6.3.6. Sponsor's justification for proposed dosing regimen – integrated analysis

6.3.6.1. Overview of the integrated analysis

[information redacted]The sponsor provided a "Justification for the Recommended Posology" based on an integrated analysis of the Week 52 efficacy and safety data from COPERNICUS and GALILEO in subjects treated only with VTE.

All subjects in COPERNICUS were eligible to receive either VTE PRN or sham injections from Week 24 through to Week 52 in accordance with protocol-defined re treatment criteria. In GALILEO, only subjects who had been randomised to VTE2Q4 were eligible to receive VTE or sham injections from Week 24 through to Week 52, with subjects who had been randomised to sham being required to continue with sham every 4 weeks from Week 24 through to Week 52. Overall, 207 subjects who had been treated with VTE2Q4 completed Week 24 of COPERNICUS/GALILEO and were eligible to enter the Week 24 to Week 52 PRN treatment period. In the Week 24 to Week 52 treatment period, the first VTE PRN injection could have been given at Week 24 and the last at Week 48. Therefore, a maximum of 7 and a minimum of 0 injections could have been given in the PRN phase. The mean number of injections administered to the 207 subjects who entered the PRN phase was 2.6 (SD = 1.7), with a median of 3.0 injections and a range of from 0 to 7 injections.

[information redacted]

In the justification analysis, the 198 subjects initially randomised to VTE who completed the full 52 weeks of the study were divided into three sub-groups depending on the number of VTE injections received fpm Week 24 to Week 52 (≤ 3 injections, 2 to 3 injections, ≥ 4 injections). In the proposed regimen, following the injection at Week 20 injections would be given at 8 week intervals resulting in 3 injections being given from Week 24 to Week 52 (that is, injections at Weeks 28, 36 and 44 with assessment at Week 52). Therefore, a comparison of the visual acuity outcomes in the sub-group of subjects receiving ≤ 3 active injections with those receiving ≥ 4 active injections was expected to provide an indication of differences in outcomes achieved with less-frequent dosing (similar to every 8 weeks) compared with more frequent dosing (similar to every 4 weeks). However, to more closely match and evaluate a potential VTE2Q8 regimen, an additional dosing sub-group of subjects receiving 2 to 3 injections was included. In this sub-group, the mean number of active injections was 2.5 (as opposed to a mean of 1.8 injections in the subjects receiving ≤ 3 active injections), which is closer to the expected 3 injections that would be administered under a VTE2Q8 regimen. Overall, the baseline demographic characteristics were generally similar for the three, non-randomised post-hoc sub-groups. The mean number of injections in the sub-groups from COPERNICUS/GALILEO are summarised below in Table 8.

Table 8: COPERNICUS/GALILEO – Number of active injections in PRN phase by dosing group; subjects completing Week 52 (n=198).

Planned treatment Number: VTE 2Q4 + PRN Wk52 compl. cut at 4 injections	n	Mean	SD	Min	Q1	Median	Q3	Max
0-3 active injections from Week 24 to Week 48	139	1.8	1.1	0	1.0	2.0	3.0	3
2-3 active injections from Week 24 to Week 48	88	2.5	0.5	2	2.0	2.5	3.0	3
4-7 active injections from Week 24 to Week 48	59	4.7	1.0	4	4.0	4.0	6.0	7

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) from week 24 to week 48.

6.3.7. Results of the integrated analysis Week 24 to Week 52 PRN period,

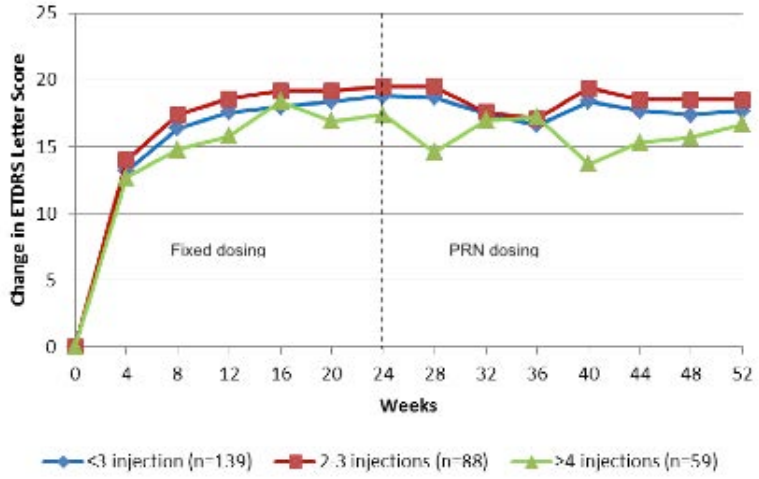
6.3.7.1. Visual acuity outcomes – BCVA letter scores

The BCVA letter scores for the three sub-groups are summarised below in Table 9 and mean changes in visual letter score from baseline over time for the three sub-groups are summarised below in Figure 3.

Table 9: Integrated analysis – BCVA letter scores; FAS/LOCF for subjects who completed Week 52 (n=198).

	n	Baseline BCVA	Week 24 BCVA		Week 52 BCVA	
			Absolute BCVA Letter Score	Change from Baseline	Absolute BCVA Letter Score	Change from Baseline
≤ 3 injections	139	51.8 ± 15.0	70.6 ± 16.0	18.8 ± 12.8	69.5 ± 18.6	17.7 ± 16.6
2 to 3 injections	88	49.3 ± 14.6	68.8 ± 15.6	19.5 ± 14.0	67.9 ± 16.3	18.5 ± 15.8
≥ 4 injections	59	51.9 ± 14.8	69.3 ± 14.1	17.4 ± 11.2	68.5 ± 15.2	16.7 ± 13.4

Figure 3: Integrated analysis – Mean changes in BCVA letter score from baseline.



Comment: All three sub-groups showed similar increases in BCVA letter scores from baseline to Week 52, with the absolute mean letter score decreasing by approximately 1 letter from Week 24 to Week 52 in each of the sub-groups. In the three sub-groups, the mean change in BCVA letter scores maximally increased from baseline at about 16 weeks after which mean change from baseline scores remained relatively stable through to Week 52. The sponsor notes that subjects receiving > 3 injections in the 6-month PRN period did not achieve better visual outcomes than subjects receiving ≤ 3 injections. However, the sub-groups were not randomised and the number of VTE doses was determined by the investigator based on perceived subject need and state of disease activity as indicated in the pre-specified re treatment criteria.

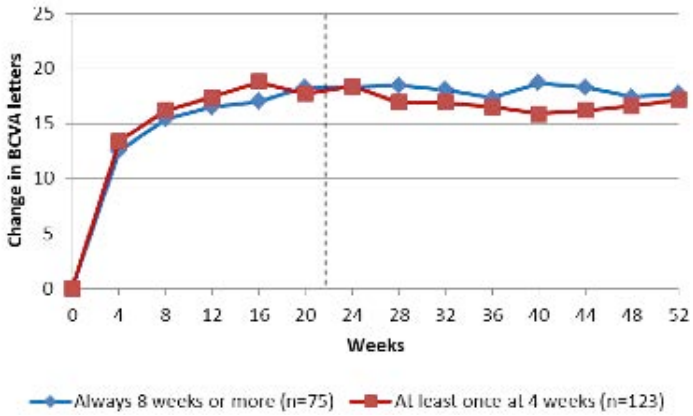
6.3.7.2. Mean number of injections in the PRN dosing period

In the PRN dosing period, 75 subjects received an injection with an interval of 8 weeks or more between injections (mean 1.2 [SD=1.0], median 1.0, range 0-2), and 123 subjects had least one 4 week interval between injections (mean 3.6 [SD=1.4], median 3.0, range 3-4). The results for the BCVA letter scores for these two groups are summarised below in Table 10 and Figure 4.

Table 10: Integrated analysis BCVA letter scores; FAS/LOCF for subjects who completed Week 52 (n=198).

	n	Absolute BCVA Letter Score Mean (SD)	Letters Score Change From Baseline Mean (SD)
Week 20			
Always ≥ 8 week intervals	75	71.5 (17.4)	18.3 (12.4)
At least one 4-week interval	123	68.8 (14.5)	17.7 (12.7)
Week 24			
Always ≥ 8 week intervals	75	71.5 (17.4)	18.3 (12.7)
At least one 4-week interval	123	69.5 (14.1)	18.4 (12.1)
Week 52			
Always ≥ 8 week intervals	75	70.9 (19.6)	17.7 (15.8)
At least one 4-week interval	123	68.2 (16.2)	17.2 (15.6)

Figure 4: Integrated analysis - Mean changes in BCVA letter score from baseline.



Comment: The results showed that there was little difference in BCVA letter scores in subjects based on the frequency of PRN dosing, with the less frequent and more frequent dosing regimens showing similar improvements in visual acuity.

6.3.7.3. Comparison of change in BCVA between fixed-dose regimen (proactive) and PRN dosing regimen (reactive)

To assess BCVA following switching subjects were divided into categories of "vision stability" defined at the last three visits in the fixed-dosing phase (i.e., weeks 16 to 24) and the last three visits in the PRN-dosing phase (Weeks 44 to 52). The total population included 207 patients, and the following categories were defined:

Excellent: Subject demonstrated a stable gain of 15 or more letters over baseline in BCVA at the three assessed visits: 78 of 107 (72.9%) subjects who were in the "excellent" category in the fixed-dosing phase were also in the "excellent" category in the PRN phase; these subjects received a median of 2 VTE injections in the PRN phase.

Good: Subject demonstrated a stable gain of 10 or more letters over baseline at the three assessed visits with all visits not showing a 15 letter or more gain: 10 of 31 (32.2%) subjects who were in the "good" category in the fixed-dosing phase were also in the "good" category in the PRN phase; these subjects received a median of 2.5 VTE injections in the PRN phase.

Modest: Subject demonstrated a stable gain of 5 or more letters at the three assessed visits with all visits not showing a 10 letter or more gain: 7 of 31 (22.6%) subjects who were in the "modest" category in the fixed-dosing phase were also in the "modest" category in the PRN phase; these subjects received a median of 2 VTE injections in the PRN phase.

Poor: Subject demonstrated a stable gain of 0 or more letters over baseline at the three assessed visits with all visits not showing a 5 letter or more gain: 3 of 15 (20.0%) subjects who were in the "poor" category in the fixed-dose phase were also in the "poor" category in the PRN phase; these subjects received a median of 6 VTE injections in the PRN phase.

No stable gain: Subject had at least one visit in the three assessed visits with a gain of fewer than 0 letters: 14 of the 19 (73.7%) of the subjects who were in the "no stable gain" group in the fixed-dose phase were also in the "no stable gain" category ain the PRN phase; these subjects received a median of 3 VTE injections in the PRN phase.

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: 1 of the 4 (25%) subjects who were in the "missing" category in the fixed-dose phase were also in the "missing" category in the PRN phase.

In addition, a regression analysis within individual subjects compared the slope of the change in BCVA at the end of the fixed-dosing phase (Weeks 16 to 24) with 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). About 32% (41/129) of the subjects with a positive slope in the fixed-dosing phase (that is, improvement in BCVA) experienced a decline in BCVA during the PRN-dosing phase while receiving a median of 3 VTE injections. Conversely, about 68% (88/129) of subjects who demonstrated a positive slope in the fixed-dosing phase (that is, improvement in BCVA) experienced an improvement (or no change) in BCVA during the PRN-dosing phase, while receiving a median of 2 VTE injections. About 61% (43/70) of the subjects who demonstrated a negative slope in the fixed-dosing phase (that is, decline in BCVA) experienced a continued decline during the PRN-dosing phase while receiving a median of 3 VTE injections. Conversely, about 38% (27/70) of subjects who demonstrated a negative slope in the fixed-dosing phase (that is, decline in BCVA) experienced an improvement (or no change) during the PRN-dosing phase, while receiving a median of 2 VTE injections.

Comment: The sponsor considers that, taken together, the data "would appear to confirm that it was largely possible to maintain the gains achieved in the first 6 months through to the end of the study with approximately 2 to 2.5 injections, which is close to the 3 injections that might have been given, for example, under a proactive Q8 regimen, thus again failing to identify a benefit for the as needed dosing". However, it is considered that no clear association between improvement in BCVA and the number of injections administered emerged from the data.

6.3.7.4. Central retinal thickness (CRT) and retinal fluid status

Following switching from proactive (Weeks 0-24) to the reactive regimen (Weeks 24-52), the mean CRT increased by approximately 35 to 40 µm from Week 24 to Week 52 in the three injection sub-groups (see Table 11, below). The proportion of subjects with a dry retina at Week 24 and Week 52 (respectively) was 80.74% and 61.76% in the ≤ 3 injections sub-group, 81.4% and 63.4% in the 2 to 3 injections sub-group, and 64.4% and 57.3% in the ≥ 4 injections sub-group.

Table 11: Integrated analysis – CRT (µm) mean (SD) by injection sub-group; FAS Week 52 completers/LOCF.

	n	Baseline CRT	Week 24 CRT		Week 52 CRT	
			Absolute CRT	Change from Baseline	Absolute CRT	Change from Baseline
≤ 3 injections	139	664 ± 223	204 ± 35	-460 ± 222	239. ± 134	-424 ± 241
2 to 3 injections	88	721 ± 222	203 ± 36	-518 ± 215	242 ± 145	-478 ± 260
≥ 4 injections	59	733 ± 243	253 ± 128	-481 ± 281	293 ± 155	-441 ± 276

The change from baseline in mean (SD) CRT at the end of the PRN dosing phase (Week 52) was notably greater in the sub-group in which subjects had received injections separated by at least one 4 week interval compared with subjects who had always received injections separated by at least 8 week intervals (see Table 12, below). However, there was a similar difference between the two sub-groups as regards mean change from baseline at Week 24 (that is, after proactive treatment) and mean change from baseline at Week 52 (that is, after switching from proactive to reactive treatment at Week 24).

Table 12: Integrated analysis – CRT (microns) mean (SD) by injection interval; FAS Week 52 completers/LOCF.

	n	Absolute CRT Mean (SD)	Change From Baseline Mean (SD)
Week 20			
Always ≥ 8 week intervals	75	203.0 (42.0)	-409.4 (215.2)
At least one 4-week interval	123	228.4 (85.0)	-499.5 (243.8)
Week 24			
Always ≥ 8 week intervals	75	203.4 (38.9)	-409.0 (212.5)
At least one 4-week interval	123	227.3 (94.3)	-500.6 (250.3)
Week 52			
Always ≥ 8 week intervals	75	251.1 (155.3)	-360.5 (217.8)
At least one 4-week interval	123	257.5 (134.0)	-470.4 (261.5)

Comment: It is considered that meaningful interpretation of the Week 52 data following PRN treatment from weeks 24 to 52 is precluded due to similar differences in mean change from baseline among the three injection groups at weeks 24 and 52, and between the two frequency sub-groups at weeks 24 and 52.

6.3.8. Long-term outlook beyond 52 weeks

The sponsor based the recommended posology on the Week 52 results for COPERNICUS and GALILEO and commented that the additional data to 100 weeks in COPERNICUS and 76 weeks in GALILEO does not change its interpretation of the preferred posology.

6.3.9. Comment

[information redacted]

The sponsor considers that the results from the PRN phase suggests "*some de-stabilization of disease and return of sign (sic) and symptoms under [the] reactive dosing paradigm*".

In the Week 24 to Week 52 reactive PRN phase, the mean (SD) number of active injections was 2.7 (1.7) with a median of 3 injections (range: 0, 7 injections) in the 207 subjects who completed the initial Week 0 to 24 proactive phase and entered the Week 24 to 52 reactive PRN phase. In the 198 subjects who completed the Week 24 to 52 reactive PRN phase, the mean (SD) time between VTE injections was 64.6 (26.9) days and the median was 60 days (range: 22, 162 days). Based on these data, [information redacted] there was no added efficacy benefit from increased PRN dosing in the Week 24 to Week 52 reactive PRN phase, the sponsor recommends an initial VTE2Q4 regimen for 6 months followed by a VTE2Q8 regimen. [information redacted].

The sponsor considers that a fixed-dose proactive regimen removes the likelihood of under-treatment occurring with a PRN regimen due to inaccurate following of pre-specified re treatment criteria, particularly over long periods of time. [information redacted].

6.4. 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 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 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 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, 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 1 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 (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 13. 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 13: COPERNICUS – Proportion of subjects who gained at least 15 letters at Weeks 24, 52, and 100; 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 ETDRS letter score at Weeks 24, 52 and 100 are summarised below in Table 14. 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 14: 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 15. 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.

Table15: 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 14.

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 16. 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 16: 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 17. 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 17: 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 18. 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 18: 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	
VTE2Q4+PRN	103	683.20 (234.46)	293.85 (173.01)	-389.35 (273.71)	-408.85	(-98.76, 10.44)	0.1122
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.

[information redacted]

7. Clinical safety

7.1. 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 adverse events (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.

7.2. Integrated summary - safety data from the Week 52 integrated database

7.2.1. Exposure

7.2.1.1. Week 0 to Week 24

In the first 24 weeks of both Phase III studies (COPERNICUS and GALILEO), subjects were scheduled to receive sham or VTE every 4 weeks (VTE2Q4), for a total of 6 injections (VTE or sham). The mean number of injections administered was similar in the two treatment groups (5.3 [SD=1.4], combined sham versus 5.7 [SD=0.9], combined VTE2Q4). The proportion of subjects receiving all 6 injections was higher in the combined VTE2Q4 group (89.0% [194/218]) than in the combined sham group (76.1% [108/142]). Mean total VTE exposure for subjects in the combined VTE2Q4 group was 11.5 mg (range: 2.0 to 12.0 mg) over a mean duration of 164.1 days (range: 28 to 185 days).

7.2.1.2. Week 24 to 52 and Week 0 to Week 52

From Week 24 to Week 52 (last treatment administered at Week 48), subjects in the sham+VTE PRN group (COPERNICUS) and VTE2Q4+PRN group (GALILEO + COPERNICUS) received active VTE injections PRN based on pre-specified re treatment criteria. The Week 24 to Week 52 sham group consisted of subjects initially randomised to sham in GALILEO who continued with monthly sham from Week 24. Subjects randomised to sham in GALILEO did not have the option to switch to VTE PRN prior to Week 52.

From Week 0 to Week 52, the mean number of injections (VTE + sham) was similar among groups (sham 10.5; sham+VTE PRN 10.5; VTE2Q4+PRN 11.9. Over 52 weeks, subjects in the combined VTE2Q4+PRN group received on average 5 more VTE injections than subjects in the sham+VTE PRN group. Mean total exposure to VTE was 6.3 mg over a mean duration of 309 days for subjects in the sham+VTE PRN group, and 16.4 mg over a mean duration of 343 days for subjects in the combined VTE2Q4+PRNgroup.

7.2.2. Baseline demographics and ocular disease characteristics (study eye)

The baseline demographic characteristics of the randomised and treated subjects in the integrated analysis were generally well balanced between the combined sham (n=142) and the combined VTE2Q4 (n=218) treatment groups. Overall, there were more males than females (204 [56.7%] versus 156 [43.3%], respectively). The mean age (all subjects) at enrollment was 64 years (range: 22, 89 years) and most subjects were White (272 [75.6%]). The demographic characteristics of subjects completing Week 24 and entering the PRN treatment phase were similar to those in the Week 0 to Week 24 treatment phase. Baseline ocular disease characteristics in the study eye were similar in the combined sham and combined VTE2Q4 treatment groups. In the total population, 82.5% (297/360) of subjects had baseline ETDRS letter scores of ≥ 35 (>20/200), with a mean (SD) baseline ETDRS letter score of 51.1 (14.9) (range: 14, 82) and a mean (SD) CRT of 666.9 (236.0) µm (range: 138, 1406).

7.2.3. Disposition

7.2.3.1. Week 0 to Week 24

The pooled population (n=366) in the integrated analysis included 145 subjects in the combined sham group and 221 subjects in the combined VTE2Q4 group. Of the total population, 142 (97.9%) subjects in the combined sham group and 218 (98.6%) subjects in the combined VTE2Q4 were randomised, with 116 (80.0%) and 206 (93.2%) subjects, respectively, completing 24 weeks of study participation. The proportion of subjects discontinuing the study drug before Week 24 was notably higher in the combined sham group than in the combined VTE2Q4 group (20.4% [n=29] versus 6.4% [n=14], respectively). The most common reason for

discontinuation of the study drug before Week 24 in the combined sham group was AE (6.3% [n=9], sham versus 1.4% [n=3], VTE2Q4), and the most common reason in the combined VTE2Q4 group was protocol violation (2.3% [n=5], VTE2Q4 versus 2.1% [n=3], sham). There were no discontinuations of the study drug before Week 24 due to treatment failure in the combined VTE2Q4 group, while 4 (2.8%) subjects in the combined sham group discontinued for this reason.

7.2.3.2. Week 0 to Week 52

The proportion of subjects who discontinued the **study drug** within the first 52 weeks was notably higher in the sham (26.5%) and sham+VTE PRN (24.3%) groups than in the combined VTE2Q4+PRN (10.6%) group (see Table 19, below).

Table 19: Integrated Analysis – Primary reason for premature discontinuation from the study drug within the first 52 weeks; all randomised subjects.

	Sham GALILEO (N=71)	Sham+VTE PRN COPERNICUS (N=74)	VTE2Q4+PRN GALILEO + COPERNICUS (N=221)	Total GALILEO + COPERNICUS (N=366)
Subjects randomized	71 (100.0)	74 (100.0)	221 (100.0)	366 (100.0)
Subjects randomized and not treated	3 (4.2)	0	3 (1.4)	6 (1.6)
Subjects randomized and treated	68 (95.8)	74 (100.0)	218 (98.6)	360 (98.4)
Subjects discontinued study drug				
No	50 (73.5)	56 (75.7)	195 (89.4)	301 (83.6)
Yes (for the following reasons)	18 (26.5)	18 (24.3)	23 (10.6)	59 (16.4)
Adverse Events	7 (10.3)	4 (5.4)	7 (3.2)	18 (5.0)
Withdrawal by Subject	3 (4.4)	1 (1.4)	7 (3.2)	11 (3.1)
Protocol Violation	2 (2.9)	2 (2.7)	5 (2.3)	9 (2.5)
Treatment Failure	5 (7.4)	4 (5.4)	0	9 (2.5)
Lost to Follow-up	0	3 (4.1)	3 (1.4)	6 (1.7)
Other	1 (1.5)	2 (2.7)	1 (0.5)	4 (1.1)
Death	0	2 (2.7)	0	2 (0.6)

7.3. Adverse events

7.3.1. Overall treatment emergent adverse event (TEAE) experience

7.3.1.1. Week 0 to Week 24

The majority of subjects in the combined sham and combined VTE2Q4 groups reported at least one TEAE (115/142 [80.9%] versus 166/218 [76.1%], respectively). The incidence of ocular TEAEs in the study eye was higher in the combined sham group (94 [66.2%]) than in the combined VTE2Q4 group (129 [59.2%]). The incidence of non-ocular TEAEs was similar in the combined sham and combined VTE2Q4 groups (75 [52.8%] versus 106 [48.6%], respectively). The incidence of injection-related ocular TEAEs in the study eye was higher in the combined VTE2Q4 group than in the combined sham group (68 [31.2%] versus 32 [22.5%], respectively). However, the incidence of serious injection-related TEAEs was low in both the combined sham and combined VTE2Q4 groups (1 [0.7%] versus 2 [0.9%], respectively). No deaths occurred in the combined VTE2Q4 group. One (1) subject in the combined sham group died as a result of a TEAE (acute MI). The overall incidence of SAEs (any) was higher in the combined sham group (25 [17.6%]) than in the combined VTE2Q4 group (18 [8.3%]), as was the incidence of TEAEs (any) leading to discontinuation of study drug (10 [7.0%] versus 3 [1.4%], respectively).

7.3.1.2. Week 24 to 52

The majority of subjects in all three groups reported at least one TEAE: 43/57 (75.4%), sham; 49/60 (81.7%), sham+VTE PRN; and 168/207 (81.2%), VTE2Q4+PRN. The incidence of ocular TEAEs in the study eye was higher in subjects in the VTE2Q4+PRN group (62.3%) than in both the sham+VTE PRN (55.0%) and the sham (50.9%) groups. The incidence of non-ocular TEAEs was higher in subjects in the sham+VTE PRN group (66.7%) than in both the VTE2Q4+PRN (56.5%) and the sham (50.9%) groups. The incidence of injection-related ocular TEAEs in the

study eye was higher in subjects in the sham+VTE PRN group (21.7%) than in both the VTE2Q4+PRN (17.4%) and sham (15.8%) groups. There were no injection-related SAEs in any subjects in the three treatment groups. No deaths occurred, and the incidence of SAEs (any) was similar in subjects in the treatment groups: 12.3% sham versus 11.7% sham+VTE PRN versus 12.1% VTE2Q4+PRN. The incidence of TEAEs (any) leading to discontinuation of study drug in subjects was low in the three treatment groups: 1.8% sham versus 0% sham+VTE PRN versus 1.9% VTE2Q4+PRN.

7.3.1.3. Week 0 to Week 52

The majority of subjects in all treatment groups reported at least one TEAE: 59/68 (86.8%), sham; 68/74 (91.9%), sham+VTE PRN; 197/218 (90.4%), VTE2Q4+PRN. The incidence of ocular TEAEs in the study eye was higher in subjects in the sham+VTE PRN group (78.4%) than in both the VTE2Q4+PRN (77.1%) and sham (72.1%) groups. The incidence of injection-related ocular TEAEs in the study eye was similar in subjects in the sham (30.9%) and sham+VTE PRN (27.0%) groups and higher in the VTE2Q4+PRN group (35.8%). There was 1 (1.5%) subject with an injection related SAE in the sham group and 2 (0.9%) subjects in the VTE2Q4+PRN group. There was 1 (1.4%) death in the sham+VTE PRN group. The incidence of SAEs was higher in subjects in the sham+VTE PRN group (28.4%) than in both the sham (20.6%) and VTE2Q4+PRN (17.9%) groups. The incidence of TEAEs (any) leading to discontinuation was lower in subjects in the VTE2Q4+PRN group (2.8%) than in both the sham+VTE PRN (6.8%) and sham (10.3%) groups.

7.3.2. Ocular treatment emergent adverse events in the study eye

7.3.2.1. Week 0 to Week 24

Ocular TEAEs reported in the study eye from Week 0 to Week 24 in ≥ 3% of subjects in either the combined sham group or the combined VTE2Q4 group are summarised below in Table 20. The highest incidence occurred in subjects in the sham/COPERNICUS group (67.6%) followed by the sham/GALILEO group (64.7%) and the combined VTE2Q4 group (59.2%). Ocular TEAES in the study eye occurring in ≥ 5% of subjects in the combined VTE2Q4 group versus sham/GALILEO versus sham/COPERNICUS were: eye pain (12.8% versus 4.4% versus 5.4%); conjunctival haemorrhage (11.9% versus 4.4% versus 17.6%); IOP increased (7.8% versus 5.9% versus 8.1%); retinal exudates (6.9% versus 7.4% versus 0%); optic disc vascular disorder (6.0% versus 4.4% versus 1.4%); retinal vascular disorder (5.5% versus 8.8% versus 5.4%); 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).

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 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%). Most TEAEs of eye pain were mild, occurred within 1 day after the first, second or third injection and resolved within 2 to 3 days. None of the TEAEs of eye pain resulted in discontinuation of the study drug.

Most ocular TEAEs in the study eye were reported with a maximum intensity of mild (combined sham, 43 [30.3%]; combined VTE2Q4, 91 [41.7%]) or moderate (combined sham, 40 [28.2%]; combined VTE2Q4, 33 [15.1%]). The incidence of severe ocular TEAEs was higher in subjects in the combined sham group (11 [7.7%]) than in the combined VTE2Q4 group (5 [2.3%]). Severe ocular TEAEs in the study eye reported by 2 or more subjects occurred in the combined sham group only and included glaucoma, macular oedema, visual acuity reduced and vitreous haemorrhage (2 subjects [1.4%] each).

Table 20: Integrated Analysis - Week 0 to Week 24, ocular TEAEs in the study eye (PT reported for ≥3% of subjects in either the combined sham or the combined VTE2Q4 group); SAF.

Primary system organ class PT (MedDRA v. 13.1)	Sham GALILEO (N=68)	Sham COPERNICUS (N=74)	VTE2Q4 GALILEO + COPERNICUS (N = 218)	Total GALILEO + COPERNICUS (N = 360)
Number of subjects with at least one ocular TEAE in study eye	**44 (64.7)**	**50 (67.6)**	**129 (59.2)[a]**	**223 (61.9)**
Eye disorders				
Conjunctival hemorrhage	3 (4.4)	13 (17.6)	26 (11.9)	42 (11.7)
Eye irritation	7 (10.3)	3 (4.1)	9 (4.1)	19 (5.3)
Eye pain	3 (4.4)	4 (5.4)	28 (12.8)	35 (9.7)
Foreign body sensation in eyes	5 (7.4)	2 (2.7)	7 (3.2)	14 (3.9)
Iris neovascularization	0	6 (8.1)	2 (0.9)	8 (2.2)
Lacrimation increased	4 (5.9)	1 (1.4)	6 (2.8)	11 (3.1)
Macular fibrosis	1 (1.5)	1 (1.4)	9 (4.1)	11 (3.1)
Macular edema	11 (16.2)	1 (1.4)	3 (1.4)	15 (4.2)
Ocular hyperemia	4 (5.9)	0	9 (4.1)	13 (3.6)
Optic disc vascular disorder	3 (4.4)	1 (1.4)	13 (6.0)	17 (4.7)
Papilloedema	3 (4.4)	2 (2.7)	4 (1.8)	9 (2.5)
Retinal exudates	5 (7.4)	0	15 (6.9)	20 (5.6)
Retinal hemorrhage	4 (5.9)	6 (8.1)	7 (3.2)	17 (4.7)
Retinal neovascularisation	3 (4.4)	2 (2.7)	1 (0.5)	6 (1.7)
Retinal vascular disorder	6 (8.8)	4 (5.4)	12 (5.5)	22 (6.1)
Visual acuity reduced	7 (10.3)	13 (17.6)	9 (4.1)	29 (8.1)
Vitreous detachment	1 (1.5)	5 (6.8)	6 (2.8)	12 (3.3)
Vitreous floaters	0	2 (2.7)	11 (5.0)	13 (3.6)
Vitreous hemorrhage	2 (2.9)	6 (8.1)	5 (2.3)	13 (3.6)
Investigations				
Intraocular pressure increased	4 (5.9)	6 (8.1)	17 (7.8)	27 (7.5)

Note: This table is summarizing all subjects with all treatment-emergent adverse events starting post first injection.

a: This value includes one VTE2Q4 subject from the GALILEO study who experienced events of dry eye in the Week 24-to-Week 52 period that were erroneously captured in the Week 0 to-Week 24 period.

7.3.2.2. Week 24 to Week 52

Ocular TEAEs reported in the study eye from Week 24 to Week 52 in ≥ 3% of subjects in either treatment group who completed Week 24 are summarised below in Table 21. The highest incidence was reported in subjects in the VTE2Q4+PRN group (62.3%) followed by the sham+VTE group (55.0%) and sham (50.9%) groups. Commonly occurring ocular TEAEs in the study eye reported more frequently in subjects in the combined VTE2Q4+PRN group than in both the sham and sham+VTE PRN groups were (respectively): macular oedema (21.3% versus 10.5% versus 0%); visual acuity reduced (13.0% versus 1.8% versus 5.0%); intraocular pressure increased (10.1% versus 3.5% versus 8.3%); cystoid macular oedema (5.8% versus 0% versus 3.3%); retinal vascular disorder (5.8% versus 5.3% versus 1.7%); eye pain (5.8% versus 3.5% versus 5.0%); vitreous detachment (5.3% versus 0% versus 1.7%); eye irritation (3.9% versus 1.8% versus 3.3%); and retinal vein occlusion (3.4% versus 0% versus 0%).

Ocular TEAEs in the study eye were most commonly reported with a maximum intensity of mild (sham, 15 [26.3%]; sham+VTE PRN, 20 [33.3%]; VTE2Q4+PRN, 62 [30%]) or moderate (sham, 12 [21.1%]); sham+VTE PRN, 12 [20.0%]; VTE2Q4+PRN, 56 [27.1%]). Severe ocular TEAEs in the study eye reported by 2 or more subjects included glaucoma (1 subject each in the sham [1.8%] and sham+VTE PRN [1.7%] groups), eye pain (2 subjects [1.0%] in the VTE2Q4+PRN group), macular oedema (2 subjects [1.0%] in the VTE2Q4+PRN group), and visual acuity reduced (3 subjects [1.4%]) in the VTE2Q4+PRN group.

Table 21: Integrated Analysis - Week 24 to Week 52, ocular TEAEs in the study eye (PTs reported for ≥3% of subjects in either treatment group); subjects who completed Week 24.

Primary system organ class PT (MedDRA v. 13.1)	Sham GALILEO (N = 57)	Sham+VTE PRN COPERNICUS (N = 60[a])	VTE2Q4+PRN GALILEO+ COPERNICUS (N = 207)	Total GALILEO+ COLPERNICUS (N = 324)
Number of subjects with at least one ocular TEAE in study eye	**29 (50.9)**	**33 (55.0)**	**129 (62.3)[b]**	**191 (59.0)**
Eye disorders				
Conjunctival hemorrhage	0	8 (13.3)	12 (5.8)	20 (6.2)
Cystoid macular edema	0	2 (3.3)	12 (5.8)	14 (4.3)
Eye irritation	1 (1.8)	2 (3.3)	8 (3.9)	11 (3.4)
Eye pain	2 (3.5)	3 (5.0)	12 (5.8)	17 (5.2)
Foreign body sensation in eyes	0	2 (3.3)	2 (1.0)	4 (1.2)
Iris neovascularization	0	2 (3.3)	3 (1.4)	5 (1.5)
Lacrimation increased	4 (7.0)	3 (5.0)	6 (2.9)	13 (4.0)
Macular cyst	2 (3.5)	1 (1.7)	2 (1.0)	5 (1.5)
Macular fibrosis	4 (7.0)	4 (6.7)	8 (3.9)	16 (4.9)
Macular edema	6 (10.5)	0	44 (21.3)	50 (15.4)
Ocular discomfort	0	2 (3.3)	2 (1.0)	4 (1.2)
Optic disc vascular disorder	3 (5.3)	2 (3.3)	7 (3.4)	12 (3.7)
Retinal degeneration	2 (3.5)	1 (1.7)	3 (1.4)	6 (1.9)
Retinal exudate	3 (5.3)	4 (6.7)	4 (1.9)	11 (3.4)
Retinal hemorrhage	5 (8.8)	3 (5.0)	12 (5.8)	20 (6.2)
Retinal neovascularization	2 (3.5)	0	2 (1.0)	4 (1.2)
Retinal pigment epitheliopathy	0	5 (8.3)	3 (1.4)	8 (2.5)
Retinal vascular disorder	3 (5.3)	1 (1.7)	12 (5.8)	16 (4.9)
Retinal vein occlusion	0	0	7 (3.4)	7 (2.2)
Retinopathy	2 (3.5)	0	2 (1.0)	4 (1.2)
Visual acuity reduced	1 (1.8)	3 (5.0)	27 (13.0)	31 (9.6)
Vitreous detachment	0	1 (1.7)	11 (5.3)	12 (3.7)
Investigations				
Intraocular pressure increased	2 (3.5)	5 (8.3)	21 (10.1)	28 (8.6)
Visual acuity tests abnormal	0	0	8 (3.9)	8 (2.5)

a: 57 subjects crossed-over to active treatment at Week 24

b: This value does not include one VTE2Q4 subject from the GALILEO study who experienced events of dry eye in the Week 24-to-Week 52 period that were erroneously captured in the Week 0 to-Week 24 period and not in the Week 24-to-Week 52 period.

Note: This table is summarizing all subjects with all treatment-emergent adverse events starting post first injection.

7.3.2.3. Week 0 to Week 52

The incidence of subjects with at least one ocular TEAE in the study eye was higher in the sham+VTE group (78.4% [58/74]) than in both the combined VTE2Q4+PRN (77.1% [168/218]) and the sham (72.1% [49/68]) groups. Ocular TEAEs in the study eye occurring in ≥ 5% of subjects in the combined VTE2Q4 PRN group versus sham versus sham+VTE were: macular oedema (21.1% versus 22.1% versus 1.4%); eye pain (15.1% versus 5.9% versus 9.5%); intraocular pressure increased (14.7% versus 5.9% versus 13.5%); visual acuity reduced (14.7% versus 11.8% versus 21.6%); conjunctival haemorrhage (14.2% versus 4.4% versus 18.9%); retinal vascular disorder (9.2% versus 11.8% versus 6.8%); ocular disc vascular disorder (9.2% versus 8.8% versus 4.1%); retinal haemorrhage (8.7% versus 11.8% versus 12.2%); retinal exudates (7.8% versus 10.3% versus 5.4%); vitreous detachment (7.8% versus 1.5% versus 8.1%); macular fibrosis (7.3% versus 7.4% versus 6.8%); vitreous floaters (6.4% versus 0% versus 4.1%); cystoid macular oedema (6.0% versus 0% versus 4.1%); and ocular hyperaemia (5.5% versus 5.9% versus 0%). Most ocular TEAEs in the study eye were reported with a maximum intensity of mild (sham, 15 [22.1%]); sham+VTE PRN, 27 [36.5%]); VTE2Q4+PRN, 83 [38.1%]) or moderate (sham, 29 [42.6%]; sham+VTE PRN, 22 [29.7%]; VTE2Q4+PRN, 70 [32.1%]).

7.3.3. Ocular treatment emergent adverse events in the fellow eye

7.3.3.1. Week 0 to Week 24

The incidence of ocular TEAEs in the fellow eye was higher in the COPERNICUS/sham group (27.0% [20/74]) than in the GALILEO/sham (14.7% [10/68]) and combined VTE2Q4 (19.7% [43/218]) groups. The incidence of ocular TEAEs in the fellow eye in the combined sham group was similar to the incidence in the combined VTE2Q4 group (21.1% [30/142] versus 19.7% [43/218], respectively). The most common ocular TEAEs in the fellow eye (combined sham group versus combined VTE2Q4 group) were: dry eye (2.8% [n=4] versus 2.3% [n=5]); retinal haemorrhage (2.1% [n=3] versus 2.3% [n=5]); and IOP increased (2.1% [n=3] versus 1.8% [n=4]). None of the ocular TEAEs in the fellow eye occurred in ≥ 3% of subjects in the combined sham or combined VTE2Q4 groups.

7.3.3.2. Week 24 to Week 52

The incidence of ocular TEAEs in the fellow eye was highest in the sham+VTE PRN group (25.0% [15/60]) followed by the combined VTE2Q4+PRN (17.4% [36/207]) and sham (8.8% [5/57]) groups. The most commonly reported TEAEs (sham versus sham+VTE PRN versus combined VTE2Q4+PRN) were: IOP increased (1.8% versus 3.3% versus 1.7%); and cataract (1.8% versus 1.7% versus 1.9%). Increased IOP was the only ocular TEAE in the fellow eye that occurred in ≥ 3% of subjects (2 subjects [3.3%], all in the sham+VTE PRN group).

7.3.3.3. Week 0 to Week 52

The incidence of ocular TEAEs in the fellow eye was highest in the sham+VTE PRN group (37.8% [28/74]) followed by the combined VTE2Q4+PRN (27.5% [60/218]) and sham (19.1% [13/68]) groups. Ocular TEAES in the fellow eye reported in ≥ 3% of subjects (sham versus sham+VTE PRN versus combined VTE2Q4+PRN) were: dry eye (0% versus 6.8% versus 2.8%); retinal haemorrhage (2.9% versus 2.7% versus 3.2%); and IOP increased (1.5% versus 5.4% versus 3.2%).

7.3.4. Non-ocular treatment emergent adverse events

7.3.4.1. Week 0 to Week 24

Non-ocular TEAEs reported in ≥ 3% of subjects in either the combined sham group or the VTE2Q4 group are summarised below in Table 22. The proportion of subjects with at least one non-ocular TEAE was higher 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 the combined sham and combined VTE2Q4 groups was nasopharyngitis (7.0% versus 6.0%, respectively).

Non-ocular TEAEs were mostly reported with a maximum intensity of mild (combined sham, 35 [24.6%]; VTE2Q4, 66 [30.3%]) or moderate (combined sham, 32 [22.5%]; VTE2Q4, 34 [15.6%]). Severe non-ocular TEAEs occurred more frequently in subjects in the combined sham group (8 [5.6%]) than in the combined VTE2Q4 group (6 [2.8%]). No severe non-ocular TEAEs occurred in more than 1 subject in either the combined sham or combined VTEQ24 treatment groups.

Table 22: Integrated Analysis – Week 0 to Week 24, non-ocular TEAEs (PTs reported for ≥ 3% of subjects in either the combined sham group or the VTE2Q4 group; SAF.

Primary system organ class Preferred term MedDRA v. 13.1	Sham GALILEO (N = 68)	Sham COPERNICUS (N = 74)	VTE2Q4 GALILEO+ COPERNICUS (N = 218)	Total GALILEO+ COPERNICUS (N = 360)
Number of subjects with at least one non-ocular TEAE	37 (54.4)[a]	38 (51.4)	106 (48.6)	181 (50.3)
Infections and infestations				
Nasopharyngitis	6 (8.8)[a]	4 (5.4)	13 (6.0)	23 (6.4)
Upper respiratory tract infection	1 (1.5)	2 (2.7)	7 (3.2)	10 (2.8)
Musculoskeletal and connective tissue disorders				
Arthralgia	5 (7.4)	1 (1.4)	2 (0.9)	8 (2.2)
Nervous system disorders				
Headache	4 (5.9)	2 (2.7)	8 (3.7)	14 (3.9)
Vascular disorders				
Hypertension	3 (4.4)	4 (5.4)	14 (6.4)	21 (5.8)

a: This value includes three sham subjects from the GALILEO study who experienced events of influenza; nasopharyngitis; and COPD, cardiac failure cronic, bronchopneumonia, and renal failure chronic, in the Week 24-to-Week 52 period that were erroneously captured in the Week 0 to-Week 24 period.
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

7.3.4.2. Week 24 to Week 52

The proportion of subjects with at least one non-ocular TEAE was higher in the sham+VTE group (66.7% [40/60]) than in both the sham (50.9% [29/57]) and VTE2Q4+PRN (56.5% [117/207]) groups. Most non-ocular TEAEs were associated with the System Organ Class (SOC) "Infections and Infestations": 18 subjects (31.6%) in the sham group; 15 subjects (25.0%) in the sham+VTE PRN group; and 50 subjects (24.2%) in the combined VTE2Q4+PRN group.

TEAEs in the SOC "Gastrointestinal Disorders" were reported more frequently in subjects in the sham+VTE PRN group (9 [15%]) than in the sham (5 [8.8%]) and combined VTE2Q4+PRN (17 [8.2%]) groups, and "Investigations" were reported more frequently in subjects in the sham+VTE PRN group (17 [28.3%]) than in the sham (3 [5.3%]) and combined VTE2Q4+PRN (17 [8.2%]) groups. The most commonly reported TEAEs in subjects in all treatment groups were: nasopharyngitis (sham, 11 [19.3%]; sham+VTE PRN, 3 [5.0%]; and combined VTE2Q4+PRN, 14 [6.8%]); and hypertension (sham, 4 [7.0%]; sham+VTE PRN, 3 [5.0%]; and combined VTE2Q4+PRN, 11 [5.3%]).

Non-ocular TEAEs were mostly reported with a maximum intensity of mild (sham, 11/57 [19.3%]; sham+VTE PRN, 20/60 [33.3%]; combined VTE2Q4+PRN, 64/207 [30.9%]) or moderate (sham, 15/57 [26.3%]; sham+VTE PRN, 15/60 [25.0%]; combined VTE2Q4+PRN, 44/207 [21.3%]). Severe non-ocular TEAEs occurred in 5.3% (3/57) of subjects in the sham group, 8.3% (5/60) of subjects in the sham+VTE PRN group and 4.3% (9/27) of subjects in the combined VTE2Q4 group. The only severe TEAE reported in more than 1 subject was syncope (2/57 [3.5%] in the sham group).

7.3.4.3. Week 0 to Week 52

The incidence of subjects with at least one non-ocular TEAE was higher in the sham+VTE PRN group (73.0% [54/74]) than in both the combined VTE2Q4+PRN (70.6% [154/218]) and sham (66.2% [45/68]) groups. Most non-ocular TEAEs were associated with the SOC "Infections and Infestations": 24 subjects (35.3%) in the sham group; 24 subjects (32.4%) in the sham+VTE PRN group; and 69 subjects (31.7%) in the combined VTE2Q4+PRN group.

7.3.5. Drug-related TEAES

7.3.5.1. Drug-related ocular TEAEs in the study eye

7.3.5.1.1. Week 0 to Week 24

The incidence of drug-related ocular TEAEs in the study eye was low in subjects in both the combined sham (4.9% [7/142]) and combined VTE2Q4 (3.7% [8/218]) groups. Only three ocular drug-related TEAEs in the study eye occurred in more than 1 subject in either treatment group: eye irritation (combined sham, 3 [2.1%]; VTE2Q4, 2 [0.9%]); endophthalmitis (combined sham, 1 [0.7%]; combined VTE2Q4, 3 [1.4%]); and IOP increased (combined sham, 6 [4.2%]; VTE2Q4, 6 [2.8%]). No other ocular drug-related TEAE occurred in more than 1 subject in either the combined sham or the combined VTE2Q4 groups.

7.3.5.1.2. Week 24 to Week 52

The incidence of drug-related ocular TEAEs in the study eye in subjects who completed Week 24 was 2.9% (6/207) in the VTE2Q4+PRN group, 1.7% (1/60) in the sham+VTE PRN group, and 0% (0/7) in the sham group. Of the 6 drug-related TEAEs in the VTE24Q+PRN group, there were 2 (1.0%) subjects with IOP increased and 1 (0.5%) subject each with cataract subcapsular, macular fibrosis, macular ischaemia, and macular fibrosis. In the sham+VTE PRN group, there was 1 subject with a drug-related cataract.

7.3.5.1.3. Week 0 to Week 52

There were a total of 26 drug-related ocular TEAEs in the study eye in a total of 21 (5.8%) subjects. The incidence of drug-related ocular TEAEs in the study eye was highest in subjects in the sham group (7.4% [5/68]), followed by the VTE2Q4+PRN (6.0% [13/218]) and the sham+VTE PRN (4.1% [3/74]) groups. The most commonly reported drug-related ocular TEAE in the study eye in the total population was IOP increased (1.7% [6/360]): 5 (1.7%) subjects in the VTE2Q4+PRN group, and 1 (1.5%) subject in the sham group. The only other drug-related ocular TEAEs in the study eye occurring in a total of 2 or more subjects were eye irritation (total of 5 [1.4%] subjects: 2 [2.9%], sham, 1 [1.4%], sham+VTE PRN, 2 [0.9%], VTE2Q4+PRN), and macular oedema (total of 2 subjects [0.6%]: 1 [1.4%], sham+VTE PRN, 1 [0.5%], VTE2Q4+PRN).

7.3.5.2. Drug-related ocular TEAEs in the fellow eye

7.3.5.2.1. Week 0 to Week 24

One (1) subject (0.7%) in the combined sham group experienced a drug-related ocular TEAE of IOP increased. No other drug-related ocular TEAEs in the fellow eye occurred in either the combined sham group or the combined VTE2Q4 group.

7.3.5.2.2. Week 24 to Week 52

There were no drug-related ocular TEAEs in the fellow eye reported from Week 24 to Week 52 in subjects who completed Week 24.

7.3.5.2.3. Week 0 to Week 52

One (1) subject (1.5%) in the sham group experienced a drug-related ocular TEAE of IOP increased. No other drug-related ocular TEAEs in the fellow eye occurred in any treatment group.

7.3.5.3. Drug-related non-ocular TEAE

7.3.5.3.1. Week 0 to Week 24

Drug-related non-ocular TEAEs occurred in 2 (1.4%) subjects in the combined sham group (acute myocardial infarction(MI) and renal failure, each reported by 1 subject [0.7%]), and 1 (0.5%) subject in the combined VTE2Q4 group (hepatic function abnormal). No other drug-

related, non-ocular TEAEs occurred in either the combined sham or combined VTE2Q4 treatment groups.

7.3.5.3.2. Week 24 to Week 52

Drug-related non-ocular TEAEs in subjects who completed Week 24 were experienced by 2 subjects (1.0%) in the VTE2Q4+PRN group (hepatic function abnormal in 1 subject [0.5%] and increased urine protein/creatinine ratio in 1 subject [0.5%]). No other drug related non-ocular TEAEs occurred in any treatment group.

7.3.5.3.3. Week 0 to Week 52

Drug-related non-ocular TEAEs were reported in 1 subject (1.5%) in the sham group (renal failure), 1 subject (1.4%) in the sham+VTE PRN group (acute MI; experienced prior to Week 24), and 2 subjects (0.9%) in the VTE2Q4+PRN group (hepatic function abnormal in 1 subject [0.5%] and increased urine protein/creatinine ratio in 1 subject [0.5%]). No other drug-related, non-ocular TEAEs occurred in any treatment group.

7.3.5.4. Ocular injection-related TEAEs in the study eye

7.3.5.4.1. Week 0 to Week 24

Ocular injection-related TEAEs reported in ≥ 3% of subjects in either the combined sham group or the combined VTE2Q4 group are summarised below in Table 23. Ocular injection-related TEAEs in the study eye most frequently occurred in subjects in the combined VTE2Q4+PRN group (31.2% [68/218]) than in the combined sham group (22.5% [32/142]). 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%).

Table 23: Integrated Analysis – Week 0 to Week 24, ocular injection related TEAEs reported in ≥ 3% of subjects in either the combined sham or the combined VTE2Q4 group; SAF.

Primary system organ class Preferred term MedDRA v 13.1	Sham GALILEO (N = 68)	Sham COPERNICUS (N = 74)	VTE2Q4 GALILEO+ COPERNICUS (N = 218)	Total GALILEO+ COPERNICUS (N = 360)
Number of subjects with at least one ocular injection-related TEAE in the study eye	18 (26.5)	14 (18.9)	68 (31.2)	100 (27.8)
Eye disorders				
Conjunctival hemorrhage	3 (4.4)	13 (17.6)	26 (11.9)	42 (11.7)
Eye irritation	7 (10.3)	1 (1.4)	6 (2.8)	14 (3.9)
Eye pain	3 (4.4)	2 (2.7)	24 (11.0)	29 (8.1)
Foreign body sensation in eyes	3 (4.4)	1 (1.4)	7 (3.2)	11 (3.1)
Ocular hyperemia	4 (5.9)	0	8 (3.7)	12 (3.3)
Investigations				
Intraocular pressure increased	2 (2.9)	0	12 (5.5)	14 (3.9)

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

7.3.5.4.2. Week 24 to Week 52

Ocular injection-related TEAEs reported in ≥ 3% of subjects who completed Week 24 in either the combined sham group or the combined VTE2Q4+PRN group are summarised below in Table 24. The incidence of injection-related ocular TEAEs in the study eye was higher in subjects in the sham+VTE PRN group (21.7%) than in both the VTE2Q4+PRN (17.4%) and sham (15.8%) groups. All commonly occurring ocular injection-related TEAEs, apart from increased lacrimation, occurred more frequently in subjects in the VTE2Q4+PRN group than in subjects in the sham group. Ocular injection-related TEAEs occurring in ≥ 2% of subjects in the VTE2Q4+PRN group (versus the sham group) were conjunctival haemorrhage (5.8% versus

0%), eye pain (4.8% versus 3.5%), eye irritation (3.4% versus 1.8%), intraocular pressure increased (2.9% versus 1.8%) and lacrimation increased (2.4% versus 7.0%).

Table 24: Integrated Analysis – Week 24 to Week 52, ocular injection-related TEAEs reported in ≥ 3% of subjects in either the combined sham or the combined VTE2Q4 group in subjects who completed Week 24.

Primary system organ class Preferred term MedDRA v 13.1	Sham (N = 57)	Sham+VTE PRN (N = 60[a])	VTE2Q4+PRN (N = 207)	Total (N = 324)
Number of subjects with at least one ocular injection-related TEAE in the study eye	**9 (15.8)**	**13 (21.7)**	**36 (17.4)**	**58 (17.9)**
Eye disorders				
Conjunctival hemorrhage	0	8 (13.3)	12 (5.8)	20 (6.2)
Eye irritation	1 (1.8)	2 (3.3)	7 (3.4)	10 (3.1)
Eye pain	2 (3.5)	2 (3.3)	10 (4.8)	14 (4.3)
Foreign body sensation in eyes	0	2 (3.3)	2 (1.0)	4 (1.2)
Lacrimation increased	4 (7.0)	3 (5.0)	5 (2.4)	12 (3.7)
Ocular discomfort	0	2 (3.3)	2 (1.0)	4 (1.2)
Investigations				
Intraocular pressure increased	1 (1.8)	0	6 (2.9)	7 (2.2)

a: 57 subjects crossed-over to active treatment at Week 24

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

7.3.5.4.3. Week 0 to Week 52

The incidence of injection-related ocular TEAEs in subjects in the study eye was higher in the VTE2Q4+PRN group (78/218 [35.8%]) than in both the sham (21/74 [30.9%]) and sham+VTE PRN (20/74 [27.0%]) groups. The most commonly occurring ocular injection-related TEAEs (≥ 5% of subjects) in the VTE2Q4+PRN group were (VTE2Q4+PRN versus sham versus sham+VTE PRN): conjunctival haemorrhage (14.2% versus 4.4% versus 18.9%); eye pain (12.4% versus 5.9% versus 5.4%); and intraocular pressure increased (7.3% versus 2.9% versus 0%). The incidence of ocular injection-related TEAEs occurring in ≥ 2% of subjects in the VTE2Q4+PRN group and in ≥ 2% more subjects than in both sham groups were (VTE2Q4+PRN versus sham versus sham+VTE PRN): eye pain (12.4% versus 5.9% versus 5.4%); vitreous floaters (3.7% versus 0% versus 1.4%); and intraocular pressure increased (7.3% versus 2.9% versus 0%).

7.3.5.5. Ocular injection-related TEAEs in the fellow eye

In the Week 0 to Week 24 period, 1 subject in the combined sham group (0.7%) experienced an eyelid function disorder in the fellow eye considered by the investigator to be related to the injection procedure in the study eye. The reason for this event was unclear. No other ocular injection-related TEAEs in the fellow eye were reported.

7.3.6. Arterial thromboembolic events

There is a theoretical risk of arterial thromboembolic (ATE) events following IVT administration of VEGF inhibitors. ATE events, as defined by the Anti-Platelet Trialists' Collaboration (APTC) criteria, include non-fatal myocardial infarction, non-fatal stroke or vascular death (including deaths of unknown cause). Post hoc adjudication of ATE events according to APTC criteria was performed by masked adjudicators. In COPERNICUS, there were no ATE/APTC events reported in the VTE2Q4 group during the first 24 weeks of treatment, while 2 subjects in the sham group experienced ATE/APTC events resulting in death during the first 24 weeks of treatment (1 x acute MI; 1 x arrhythmia). From Week 24 to Week 52, 1 subject in the VTE2Q4+PRN group (COPERNICUS) experienced an ATE/APTC event of non-fatal MI. No ATE/APTC events were reported in GALILEO from Week 0 to Week 52.

7.3.7. Deaths and serious adverse events

7.3.7.1. Deaths

There were total of two deaths, both of which occurred in COPERNICUS, in subjects treated with sham and both of which were considered to be ATE/APTC events. One (1) subject treated with

sham died as a result of a drug-related TEAE (acute MI) in the first 24 weeks of treatment (3 days after the last dose of study drug). One (1) subject treated with sham died as a result of arrhythmia 54 days after the last dose of study medication. This death was not considered to be treatment emergent and was adjudicated as a vascular death.

7.3.8. Serious adverse events (SAEs)

7.3.8.1. Serious ocular TEAEs in the study eye

7.3.8.1.1. Week 0 to Week 24

Serious ocular TEAEs in the study eye are summarised below in Table 25. The incidence of serious ocular TEAEs in the study eye was higher in subjects in the combined sham group (10.6%) than in the combined VTE2Q4 group (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: vitreous haemorrhage (5 [3.5%]); glaucoma (3 [2.1%]); and iris neovascularisation, macular edema, visual acuity reduced, and retinal haemorrhage (2 [1.4%] each). One (1) subject (0.5%) in the combined VTE2Q4 group experienced an SAE of endophthalmitis compared with no subjects in the combined sham group. There were no reports of SAEs of macular oedema in the combined VTE2Q4 group, compared with 2 subjects (1.4%) in the combined sham group.

Table 25: Integrated Analysis – Week 0 to Week 24, serious ocular TEAEs in the study eye; SAF.

Primary system organ class Preferred term (MedDRA v. 13.1)	Sham GALILEO (N = 68)	Sham COPERNICUS (N = 74)	VTE2Q4 GALILEO+ COPERNICUS (N = 218)	Total GALILEO+ COPERNICUS (N = 360)
Number of subjects with at least one serious ocular TEAE in study eye, n (%)	**5 (7.4)**	**10 (13.5)**	**6 (2.8)**	**21 (5.8)**
Eye disorders	**5 (7.4)**	**10 (13.5)**	**4 (1.8)**	**19 (5.3)**
Glaucoma	1 (1.5)	2 (2.7)	0	3 (0.8)
Iris neovascularisation	0	2 (2.7)	1 (0.5)	3 (0.8)
Macular edema	2 (2.9)	0	0	2 (0.6)
Retinal artery occlusion	0	0	1 (0.5)	1 (0.3)
Retinal hemorrhage	0	2 (2.7)	0	2 (0.6)
Retinal tear	0	1 (1.4)	0	1 (0.3)
Retinal vein occlusion	0	1 (1.4)	1 (0.5)	2 (0.6)
Visual acuity reduced	1 (1.5)	1 (1.4)	0	2 (0.6)
Vitreous detachment	0	0	1 (0.5)	1 (0.3)
Vitreous hemorrhage	1 (1.5)	4 (5.4)	0	5 (1.4)
Infections and infestations	**0**	**0**	**1 (0.5)**	**1 (0.3)**
Endophthalmitis	0	0	1 (0.5)	1 (0.3)
Injury, poisoning and procedural complications	**0**	**0**	**1 (0.5)**	**1 (0.3)**
Corneal abrasion	0	0	1 (0.5)	1 (0.3)

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

7.3.8.1.2. Week 24 to Week 52

Serious ocular TEAEs in the study eye reported in subjects who completed Week 24 are summarised below in Table 26. Serious ocular TEAEs in the study eye were reported more frequently in subjects in the VTE2Q4+PRN group (5.3%) than in both the sham (3.5%) and sham+VTE PRN (3.3%) groups. 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 by 2 or more subjects occurred in the VTE2Q4+PRN group only: macular edema (4 [1.9%]); vitreous haemorrhage, and retinal vein occlusion (2 [1.0%] each).

Table 26: Integrated Analysis – Week 24 to Week 52, serious ocular TEAEs in the study eye; subjects who completed Week 24.

Primary system organ class Preferred term (MedDRA v. 13.1)	Sham GALILEO (N = 57)	Sham+VTE PRN COPERNICUS (N = 60[a])	VTE2Q4+PRN GALIEO+ COPERNICUS (N = 207)	Total GALIEO+ COPERNICUS (N = 324)
Number of subjects with at least one serious ocular TEAE in the study eye, n (%)	**2 (3.5)**	**2 (3.3)**	**11 (5.3)**	**15 (4.6)**
Eye disorders	**2 (3.5)**	**2 (3.3)**	**11 (5.3)**	**15 (4.6)**
Cataract	0	1 (1.7)	1 (0.5)	2 (0.6)
Cystoid macular edema	0	0	1 (0.5)	1 (0.3)
Glaucoma	1 (1.8)	1 (1.7)	0	2 (0.6)
Macular fibrosis	0	0	1 (0.5)	1 (0.3)
Macular ischemia	0	0	1 (0.5)	1 (0.3)
Macular edema	0	0	4 (1.9)	4 (1.2)
Retinal tear	0	1 (1.7)	0	1 (0.3)
Retinal vein occlusion	0	0	2 (1.0)	2 (0.6)
Visual acuity reduced	0	0	1 (0.5)	1 (0.3)
Vitreous hemorrhage	1 (1.8)	1 (1.7)	2 (1.0)	4 (1.2)

a: 57 subjects crossed-over to active treatment at Week 24
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

7.3.8.1.3. Week 0 to Week 52

The incidence of serious ocular TEAEs (SAF) in the study eye from Week 0 to Week 52 was higher in subjects in the sham+VTE PRN group (12/74 [16.2%]) than in both the sham (6/68 [8.8%]) and the VTE2Q4+PRN (16/218 [7.3%] groups. The most frequently reported serious ocular TEAE in the study eye in the VTE2Q4+PRN group was macular oedema which was reported in 4 subjects (1.8%), compared with 2 subjects (2.9%) in the sham group and no subjects in the sham+VTE PRN group. The only other serious ocular TEAEs in the study eye reported in 2 or more subjects in the VTE2Q4+PRN group were retinal vein occlusion (2 [0.9%], VTE2Q4+PRN; 0 [0%], sham; 1 [1.4%], sham+VTE PRN), and vitreous haemorrhage (2 [0.9%], VTE2Q4+PRN; 1 [1.5%], sham; 5 [6.8%], sham+VTE PRN).

7.3.8.1.4. Serious ocular TEAEs in the fellow eye

In weeks 0-24, no serious ocular TEAEs in the fellow eye occurred in either the combined sham or the combined VTE2Q4 group. In weeks 0-52, 1 serious ocular TEAE in the fellow eye occurred in the VTE2Q4+PRN group (vitreous haemorrhage).

7.3.8.2. Serious non-ocular TEAEs

7.3.8.2.1. Week 0 to Week 24

The incidence of serious non-ocular TEAEs was higher in subjects in the combined sham group than in the combined VTE2Q4 group (11 [7.7%] versus 12 [5.5%], respectively). Pneumonia was the only serious non-ocular TEAE reported by more than 1 subject (combined sham group, 2 subjects [1.4%]). Circulatory collapse was predefined as a systemic reaction related to immunogenicity. However, the 1 subject in the combined VTE2Q4 group who experienced a serious TEAE of circulatory collapse had negative results in the anti-drug antibody (ADA) assay.

7.3.8.2.2. b. Week 24 to Week 52

The incidence of serious non-ocular TEAEs was lower in subjects in the VTE2Q4+PRN group (13 [6.3%]) than in both the sham+VTE PRN (5 [8.3%]) and sham (5 [8.8%]) groups. No serious non-ocular TEAEs occurred in 2 or more subjects in the VTE2Q4+PRN group.

7.3.8.2.3. Week 0 to Week 52

The incidence of serious non-ocular TEAEs was lower in subjects in the VTE2Q4+PRN group (24 [11.0%]) than in both the sham (9 [13.2%]) and sham+VTE PRN (10 [13.5%] groups. No serious non-ocular TEAEs occurred in 2 or more subjects in the VTE2Q4+PRN group.

7.3.8.3. Serious ocular drug-related TEAEs

The occurrence of serious non-ocular drug-related TEAEs was rare. Over the full 52-weeks of the studies only 3 subjects experienced serious drug-related ocular TEAEs: 1 subject [VTE2Q4], retinal artery occlusion prior to Week 24; 1 subject [VTE2Q4], macular ischaemia prior to Week 24; 1 subject [VTE2Q4+PRN], cataract after Week 24).

7.3.8.4. Serious non-ocular drug-related TEAEs

The occurrence of serious non-ocular drug-related TEAEs was rare. Over the full 52 weeks of the studies only 3 subjects experienced serious drug-related non-ocular TEAEs: renal failure (prior to Week 24; sham); acute MI (prior to Week 24; sham); and hepatic function abnormal (after Week 24; VTE2Q4+PRN).

7.3.8.5. Serious ocular injection-related TEAEs

The occurrence of serious ocular injection-related TEAEs was rare. Over the full 52-weeks of the studies only 3 subjects experienced serious ocular injection-related TEAEs: endophthalmitis (prior to Week 24; VTE2Q4); vitreous haemorrhage (prior to Week 24; sham), and vitreous detachment (prior to Week 24; VTE2Q4).

7.3.9. Discontinuation of the study drug due to treatment related adverse events

7.3.9.1. Week 0 to Week 24

TEAEs leading to discontinuation of the study drug are summarised below in Table 27. The incidence of TEAEs leading to discontinuation of the study drug was higher in subjects in the combined sham group (10 [7.0%]) than in the combined VTE2Q4 group (3 [1.4%]). No TEAEs leading to discontinuation of more than 1 subject were reported in the combined VTE2Q4 group.

Table 27: Integrated Analysis – Week 0 to Week 24, TEAEs leading to discontinuation of the study drug; SAF.

Primary system organ class Preferred term (MedDRA v. 13.1)	Sham GALILEO (N = 68)	Sham COPERNICUS (N = 74)	VTE2Q4 GALILEO+ COPERNICUS (N = 218)	Total GALILEO+ COPERNICUS (N = 360)
Number of subjects with at least one TEAE causing discontinuation of study drug	**5 (7.4)**	**5 (6.8)**	**3 (1.4)**	**13 (3.6)**
Eye disorders	**5 (7.4)**	**5 (6.8)**	**2 (0.9)**	**12 (3.3)**
Corneal edema	1 (1.5)	0	0	1 (0.3)
Glaucoma	1 (1.5)	1 (1.4)	0	2 (0.6)
Iris neovascularisation	0	1 (1.4)	1 (0.5)	2 (0.6)
Macular edema	1 (1.5)	0	0	1 (0.3)
Retinal artery occlusion	0	0	1 (0.5)	1 (0.3)
Retinal hemorrhage	1 (1.5)	1 (1.4)	0	2 (0.6)
Retinal neovascularisation	3 (4.4)	0	0	3 (0.8)
Retinal tear	0	1 (1.4)	0	1 (0.3)
Visual acuity reduced	0	1 (1.4)	0	1 (0.3)
Vitreous hemorrhage	0	2 (2.7)	0	2 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**1 (0.5)**	**1 (0.3)**
Non-small cell lung cancer	0	0	1 (0.5)	1 (0.3)

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

7.3.9.2. Week 24 to Week 52

TEAEs leading to discontinuation of the study drug in subjects who completed Week 24 are summarised below in Table 28.

Table 28: Integrated Analysis – Week 0 to Week 24, TEAEs leading to discontinuation of the study drug; SAF.

Primary system organ class Preferred term (MedDRA v. 13.1)	Sham GALILEO (N = 57)	Sham+VTE PRN COPERNICUS (N = 60[a])	VTE2Q4+PRN GALILEO + COPERNICUS (N = 207)	Total GALILEO + COPERNICUS (N = 324)
Number of subjects with at least one TEAE causing discontinuation of study drug; n (%)	**2 (3.5)**	**0**	**5 (2.4)**	**7 (2.2)**
Eye disorders	**2 (3.5)**	**0**	**4 (1.9)**	**6 (1.9)**
Glaucoma	1 (1.8)	0	0	1 (0.3)
Iris neovascularisation	0	0	1 (0.5)	1 (0.3)
Macular ischemia	0	0	1 (0.5)	1 (0.3)
Macular edema	1 (1.8)	0	0	1 (0.3)
Retinal vein occlusion	0	0	1 (0.5)	1 (0.3)
Vitreous hemorrhage	0	0	1 (0.5)	1 (0.3)
Hepatobiliary disorders	**0**	**0**	**1 (0.5)**	**1 (0.3)**
Hepatic function abnormal	0	0	1 (0.5)	1 (0.3)

a: 57 subjects crossed over to active treatment at Week 24

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

7.3.9.3. Week 0 to Week 52

The incidence of TEAEs leading to discontinuation of the study drug was higher in subjects in the sham group (7 [10.3%]) than in both the sham+VTE PRN (5 [6.8%]) and VTE2Q4+PRN (8 [3.7%]) groups. TEAEs leading to study drug discontinuation of subjects in the sham group were: retinal neovascularisation (3 [4.9%]); glaucoma and macular oedema (2 each [2.9%]); and corneal oedema and retinal haemorrhage (1 each [1.8%]). TEAEs leading to study drug discontinuation in subjects in the sham+VTE PRN group were: vitreous haemorrhage (2 [2.7%]); iris neovascularisation, glaucoma, retinal haemorrhage, retinal tear and visual acuity reduced (1 each [1.4%]). TEAEs leading to study drug discontinuation in subjects in the VTE2Q4+PRN group were: iris neovascularisation (2 [0.9%]); macular ischaemia, retinal vein occlusion, retinal artery occlusion, NSCLC, vitreous haemorrhage and hepatic function abnormal (1 [0.5%] each).

7.3.10. Treatment emergent adverse events of interest

7.3.10.1. Ocular TEAEs of interest in the study eye

7.3.10.1.1. Week 0 to Week 24

The overall incidence of ocular TEAEs of interest in the study eye was higher in subjects in the combined sham group (51/142 [35.9%]) than in the combined VTE2Q4 group (64/218 [29.4%]). The most common (≥ 5% overall) ocular TEAEs of interest in subjects in the combined VTE2Q4 group (versus combined sham) were: subconjunctival/conjunctival haemorrhage (26 [11.9%] versus 14 [9.9%]); mild transient pain at the injection site (26 [11.9%] versus 7 [4.9%]); transient increase in IOP (13 [6.0%] versus 2 [1.4%]); and any clinically significant decrease in BCVA (13 [6.0%] versus 23 [16.2%]).

Common categories (≥ 5%) of ocular TEAEs of interest in subjects in the combined VTE2Q4 group with an incidence of more than twice that in the combined sham group included only mild transient pain at the injection site (26 [11.9%] versus 7 [4.9%]). Common categories (≥ 5%) of ocular TEAEs of interest in the study eye in subjects in the combined sham group with an incidence of more than twice that in the combined VTE2Q4 group included only clinically significant decrease in BCVA (23 [16.2%] versus 13 [6.0%]).

Two (2) subjects (1.4%) in the combined sham group experienced IOP ≥ 35 mmHg requiring treatment (versus no subjects in the VTE2Q4 group); 9 subjects experienced new onset, elevated IOP requiring treatment (6 [4.2%], combined sham versus 3 [1.4%], combined VTE2Q4); and 15 subjects experienced transient increases in IOP (2 [1.4%], combined sham versus 13 [6.0%], combined VTE2Q4).

7.3.10.1.2. Week 24 to Week 52

The overall incidence of ocular TEAEs of interest in subjects in the study eye was higher in the VTE2Q4+PRN group (57 [27.5%]) than in both the sham+VTE PRN (14 [23.3%]) and sham (6 [10.5%] groups. The most commonly reported TEAE (≥ 5%) of interest in the study eye in subjects in the VTE2Q4+PRN group (VTE2Q4 versus sham versus sham+VTE PRN) was visual acuity reduced (13.0% versus 1.8% versus 5.0%).

Common categories (≥ 5%) of ocular TEAEs of interest in subjects in the VTE2Q4+PRN group with an incidence of more than twice that in either sham group (VTE2Q4+PRN versus sham versus sham+VTE PRN) included only any clinically significant decrease in BCVA (15.5% versus 1.8% versus 5.0%). Common categories (≥ 5%) ocular TEAEs of interest in subjects in the sham+VTE PRN group with an incidence of more than twice that in either of the other two groups (sham+VTE PRN versus sham versus VTE2Q4+PRN) included only subconjunctival/conjunctival haemorrhage (13.3% versus 0% versus 6.3%). There were no common categories (≥ 5%) of ocular TEAEs of interest in the sham group with an incidence of more than twice that in either of the two other groups (that is, sham+VTE PRN and VTE2Q4+PRN). The incidence of new onset, elevated IOP requiring treatment was similar in the three treatment groups: sham, 2 subjects (3.5%); sham+VTE PRN, 2 subjects (3.3%); and VTE2Q4+PRN, 8 subjects (3.9%).

7.3.10.1.3. Week 0 to Week 52

The overall incidence of ocular TEAEs of interest in the study eye was higher in subjects in the sham+VTE PRN (35 [47.3%]) and VTE2Q4+PRN (90 [41.3%]) groups than in the sham group (25 [36.8%]). Common (≥5%) ocular TEAEs of interest in subjects in the VTE2Q4+PRN group were conjunctival haemorrhage (30 [13.8%]), eye pain (27 [12.4%]), visual acuity reduced (32 [14.7%]), and IOP increased (16 [7.3%]). Common (≥ 5%) ocular TEAEs of interest in subjects in the sham group were eye pain (4 [5.9%]) and visual acuity reduced (8 [11.8%]). Common (≥5%) ocular TEAEs of interest in subjects in the sham+VTE PRN group were visual acuity reduced (16 [21.6%]), IOP increased (5 [6.8%]), eye pain (4 [5.4%]) and conjunctival haemorrhage (13 [17.6%]). The incidence of new onset elevated IOP requiring treatment was similar in subjects in the three treatment groups (sham, 4 [5.9%]; sham+VTE PRN, 5 [6.8%]; VTE2Q4+PRN, 10 [4.6%]).

7.3.10.2. Ocular TEAEs of interest in the fellow eyes

During the 52 weeks of the studies, ocular TEAEs (SAF) of interest in the fellow eye were reported in 2/68 subjects (2.9%) in the sham group, 2/74 subjects in the sham+VTE PRN group and 3/218 subjects (1.4%) in the VTE2Q4+PRN group. All ocular TEAEs of interest in the fellow eye in the three treatment groups were categorised as new onset elevated IOP requiring treatment.

7.3.10.3. Non-ocular TEAEs of interest

7.3.10.3.1. Week 0 to Week 24

Non-ocular TEAEs of interest with potential clinical significance are summarised below in Table 29. Non-ocular TEAEs of interest occurred in the same proportion of subjects in the combined sham and combined 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 combined VTE2Q4 group compared with the combined sham group (6.4% versus 4.9%, respectively). The only other non-ocular TEAE of interest reported in 2 or more subjects in the

combined VTE2Q4 group was blood pressure increased (2 subjects, 0.9%) and this event occurred more frequently in the combined sham group (2 subjects, 1.4%).

Table 29: Integrated Analysis – Week 0 to Week 24, non-ocular TEAEs of interest; SAF.

Primary system organ class Preferred term (MedDRA v. 13.1)	Sham GALILEO (N = 68)	Sham COPERNICUS (N = 74)	VTE2Q4 GALILEO+ COPERNICUS (N = 218)	Total GALILEO+ COPERNICUS (N = 360)
Number of subjects with at least one non-ocular TE AEI	4 (5.9)	9 (12.2)	20 (9.2)	33 (9.2)
Arterial thromboembolic events	0	2 (2.7)	1 (0.5)	3 (0.8)
Acute myocardial infarction	0	1 (1.4)	0	1 (0.3)
Carotid artery stenosis	0	1 (1.4)	1 (0.5)	2 (0.6)
Embryo-fetotoxicity[a]	0	1 (1.4)	1 (0.5)	2 (0.6)
Arnold-Chiari malformation	0	1 (1.4)	0	1 (0.3)
Gilbert's syndrome	0	0	1 (0.5)	1 (0.3)
Erosions & ulcerations of nasal mucosa	0	0	1 (0.5)	1 (0.3)
Epistaxis	0	0	1 (0.5)	1 (0.3)
Hypertension	3 (4.4)	6 (8.1)	16 (7.3)	25 (6.9)
Blood pressure increased	0	2 (2.7)	2 (0.9)	4 (1.1)
Hypertension	3 (4.4)	4 (5.4)	14 (6.4)	21 (5.8)
Systemic reactions related to immunogenicity	1 (1.5)	0	2 (0.9)	3 (0.8)
Circulatory collapse	1 (1.5)[b]	0	1 (0.5)[c]	2 (0.6)
Urticaria	0	0	1 (0.5)	1 (0.3)

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.
a: No pregnancies occurred during the first 24 weeks of the study. All events represent pre-existing congenital conditions that were present at baseline in the subjects, not their offspring. The conditions were reported as TEAEs because of episodic worsening or chance findings in laboratory tests.
b: This event was not due to immunogenicity. Although the subject had positive results in the ADA assay, the subject had received no VEGF Trap-Eye and the positive ADA results were due to high background responses in the ADA assay or a pre-existing immunoreactivity to VEGF Trap-Eye.
c: This event was not due to immunogenicity (the subject had ADA negative results at all time points) but may have been due to the subject's underlying cardiovascular conditions (Module 5.3.5.1 GALILEO 24-week CSR (A52377) Section 11).

7.3.10.3.2. Week 24 to Week 52

Non-ocular TEAEs of interest in subjects who completed Week 24 are summarised below in Table 30. The incidence of non-ocular TEAEs of interest was higher in subjects in the sham+VTE PRN group than in both the sham and VTE2Q4+PRN groups (13.3% versus 8.8% versus 7.2%, respectively). The only non-ocular TEAEs of interest occurring in more than two subjects were hypertension (4 subjects [7.0%], sham; 3 subjects [5.0%], sham+VTE PRN; 11 subjects [5.3%], VTE2Q4 PRN), and blood pressure systolic increased (3 subjects [5.0%], sham+VTE PRN; 1 subject [0.5%], VTE2Q4+PRN).

Table 30: Integrated Analysis – Week 24 to Week 52, non-ocular TEAEs of interest; Week 24 completers.

AEI category/ AEI group Preferred term (MedDRA v 14.1)	Sham GALILEO (N = 57)	Sham+VTE PRN COPERNICUS (N = 60[a])	VTE2Q4+PRN GALILEO + COPERNICUS (N = 207)	Total GALILEO + COPERNICUS (N = 324)
Number of subjects with at least one non-ocular TE AEI	**5 (8.8)**	**8 (13.3)**	**15 (7.2)**	**28 (8.6)**
Adverse events of interest	**5 (8.8)**	**8 (13.3)**	**15 (7.2)**	**28 (8.6)**
Arterial thromboembolic events	**2 (3.5)**	**0**	**2 (1.0)**	**4 (1.2)**
Cerebral infarction	1 (1.8)	0	0	1 (0.3)
Myocardial infarction	0	0	2 (1.0)	2 (0.6)
Transient ischemic attack	1 (1.8)	0	0	1 (0.3)
Vascular encephalopathy	1 (1.8)	0	0	1 (0.3)
Erosions and ulcerations of nasal mucosa	**0**	**0**	**2 (1.0)**	**2 (0.6)**
Epistaxis	0	0	2 (1.0)	2 (0.6)
Hypertension	**4 (7.0)**	**8 (13.3)**	**12 (5.8)**	**24 (7.4)**
Blood pressure increased	0	2 (3.3)	0	2 (0.6)
Blood pressure systolic increased	0	3 (5.0)	1 (0.5)	4 (1.2)
Hypertension	4 (7.0)	3 (5.0)	11 (5.3)	18 (5.6)

a: 57 subjects crossed over to active treatment at Week 24

Note: Additional restrictions are applied to individual AEI groupings as defined in the document '2011032 9 Detailed Definitionof AEI and Selected Sub-groups_v1.1.pdf'.

Note: At each level of subject summarization, a subject is counted once if the subject reported one or mo re events.

7.3.10.3.3. Week 0 to Week 52

The overall incidence of non-ocular TEAEs of interest was higher in subjects in the sham+VTE PRN group (16 [21.6%]) than in both the sham (7 [10.3%]) and VTE2Q4+PRN (32 [14.7%]) groups. Non-ocular TEAEs of interest occurring in more than two subjects were: hypertension (6 subjects [8.8%], sham; 7 subjects [9.5%], sham+VTE PRN; 24 subjects [11.0%], VTE2Q4+PRN); epistaxis (3 subjects [1.4%], VTE2Q4+PRN); blood pressure systolic increased (3 subjects [4.1%], sham+VTE PRN; 1 subject [0.5%], VTE2Q4+PRN); and blood pressure increased (3 subjects [4.1%], sham+VTE PRN; 2 subjects [0.9%], VTE2Q4+PRN).

7.3.11. Serious ocular (study eye) and serious non-ocular TEAEs of interest

7.3.11.1. Week 0 to Week 24 (SAF)

There were 2/218 subjects (0.9%) in the combined VTE2Q4 group with serious TEAEs of interest (1 subject with systemic reaction [circulatory collapse] related to immunogenicity; 1 subject with endophthalmitis due to IVT injection procedure). However, the event of circulatory collapse could not have been due to immunogenicity as the subject had ADA negative results at all time points but may have been due to underlying cardiovascular conditions. In the combined sham group there were 5/142 subjects (3.5%) with serious TEAEs of special interest: 2 (1.4%) with visual acuity reduced; and 1 (0.7%) each with vitreous haemorrhage, acute MI, and carotid artery stenosis.

7.3.11.2. Week 24 to Week 52

In subjects who completed Week 24, there were 2/207 (1.0%) subjects in the VTE2Q4+PRN group with serious TEAEs of interest (1 with MI and 1 with visual acuity reduced). There was 1/57 (1.8%) subjects in the sham group with a serious TEAE of interest (transient ischaemic attack), and no (0/60) subjects in the sham+VTE PRN group with serious TEAEs of interest.

7.3.11.3. Week 0 to Week 52

Serious ocular (study eye) or non-ocular TEAEs were reported in: 4/218 (1.8%) subjects in the VTE2Q4+PRN group (1 [0.5%] for each of MI, circulatory collapse, visual acuity reduced, or endophthalmitis due to IVT injection procedure); 3/68 (4.4%) subjects in the sham group (1

[1.5%] for each of transient ischaemic attack, visual acuity reduced, or vitreous haemorrhage); 3/74 (4.1%) subjects in the sham+VTE PRN group (1 [1.4%] for each of acute MI, MI or reduced visual acuity).

7.4. Laboratory tests

7.4.1. Haematology

There were no obvious trends in mean or median haematology values measured from baseline to Week 24 in either the combined sham group or the combined VTE2Q4 group, and from baseline to Week 52 in the sham, sham+VTE PRN, or VTE2Q4+PRN groups. The majority of subjects with haematology values (haematocrit, haemoglobin, red blood cell counts (RBC), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH) and Mean Corpuscular Haemoglobin concentration (MCHC)) had normal values at Weeks 12, 24, 36 and 52. The percentage of subjects with individual haematology variables that shifted from normal at baseline to abnormal at Weeks 12, 24, 32 or 52 was similar for the treatment groups. There were no significant differences in pre-defined clinically meaningful haematology laboratory abnormalities at Week 24 between the combined sham and the combined VTE2Q4 groups or at Week 52 across the sham, sham+VTE PRN, and VTE2Q4+PRN groups.

7.4.2. Clinical chemistry

There were no trends in mean or median clinical chemistry values measured from baseline to Week 24 in either the combined sham group or the combined VTE2Q4 group and from baseline to Week 52 in the sham, sham+VTE PRN, or VTE2Q4+PRN groups. The majority of subjects (≥ 70 %) in the pooled analysis set had normal chemistry values at baseline and maintained these values at Weeks 12, 24, 36 and 52. There were no notable differences in pre-defined clinically meaningful clinical chemistry abnormalities at Week 24 between the combined sham and the combined VTE2Q4 groups or at Week 52 across the sham, sham+VTE PRN and VTE2Q4+PRN groups. In particular, there was no evidence that treatment with VTE was associated with renal or liver function abnormalities.

7.4.3. Urinalysis

There were no clinically meaningful differences in the urinalysis results among the treatment groups. In the Week 24 data, the proportion of subjects with urine protein/creatinine ratio values above the upper limit of normal (ULN) was higher in the combined sham group (28.1%) than in the combined VTE2Q4 group (8.5%).

7.5. Other observations relating to safety

7.5.1. Vital signs

There were no clinically meaningful changes in blood pressure, pulse rate or temperature in the treatment groups from baseline to Week 52.

7.5.2. Ocular safety measures

7.5.2.1. Slit lamp biomicroscopy, gonioscopy, indirect ophthalmoscopy

In both COPERNICUS and GALILEO, extensive ophthalmic examinations were conducted in all subjects at monthly intervals through to Week 52. These included slit lamp biomicroscopy of the lids, conjunctiva, iris, pupils, lens and vitreous body. In GALILEO, gonioscopy was conducted in conjunction with a slit lamp microscope. Indirect ophthalmoscopy was also conducted pre-injection.

Very few subjects in any of the three treatment groups had cells in the anterior chamber of the study eye from week 4 through to Week 52. No finding in the VTE groups were more than trace cells.

Very few subjects in the sham (1 at Week 12 and 1 at week 36) and sham+VTE PRN (1 at Week 12) groups had an anterior chamber flare in the study eye from week 4 through to Week 52. No subject in the VTE2Q4+PRN group had an anterior chamber flare in the study eye from week 4 through to Week 52.

Few subjects in any of the three treatment groups had cells in the vitreous of the study eye from Week 4 through to Week 52. One subject in the sham group had 2+ vitreous cells (Week 24), one subject in the sham+VTE PRN had 2+ vitreous cells (Week 36) and one subject in the sham group had 3+ vitreous cells (Week 4) in the study eye at a single time point. All other reports in any treatment group were trace or 1+ in severity.

Notable ophthalmic findings were limited to neovascularisation. The incidence of treatment-emergent iris neovascularisation at Week 24 was higher in the combined sham group (6 subjects [4.2%]) than in the combined VTE2Q4 group (2 subjects [0.9%]). Two (2) subjects (1 combined sham; 1 combined VTE2Q4) discontinued study treatment before Week 24 because of iris neovascularisation. At Week 52, the incidence of treatment-emergent iris neovascularisation was higher in the sham+VTE PRN group (6 subjects [8.1%]) than in the VTE2Q4+PRN group (5 subjects [2.3%]). There were no events of iris neovascularisation at Week 52 in the sham group. Between Week 24 and Week 52, 1 additional subject in the VTE2Q4+PRN group discontinued study treatment because of iris neovascularisation.

7.5.2.2. Intraocular pressure

Pre-injection mean IOP was similar in the three treatment groups at baseline (sham 14.4 mmHg; sham+VTE PRN 14.9 mmHg; VTE2Q4+PRN 15.1 mm Hg) and in all groups IOP was considered to be normal. At Week 52, small clinically insignificant increases in IOP from baseline were reported (1.0 mmHg, sham; 1.1 mmHg, sham+VTE PRN; 0.4 mmHg, VTE2Q4+PRN).

The proportion of subjects with ≥10 mmHg increases in pre-dose IOP from baseline occurring at least once during: (a) the first 24 weeks was greater in subjects in the combined sham group (10 [7.0%]) than in the combined VTE2Q4 group (6 [2.8%]); and (b) between Week 24 and Week 52 was higher in subjects in subjects in the sham+VTE PRN (6 [10.0%]) and VTE2Q4+PRN (14 [6.8%]) groups than in the sham group (2 [3.5%]).

The proportion of subjects with a pre-dose absolute IOP value >21 mmHg: (a) over the course of the first 24 weeks was greater in the combined sham group (17 [12.0%]) than in the combined VTE2Q4 group (19 [8.7%]); and (b) at any time-point from Week 24 to Week 52 was higher in subjects in the sham+VTE PRN group (13 [21.7%]) than in the sham (6 [10.5%]) and VTE2Q4+PRN (30 [14.5%]) groups.

A pre-dose absolute IOP value of ≥35 mmHg was reported for: (a) 1 subject each at Weeks 8, 20, and 24 in the combined sham group and for no subjects in the combined VTE2Q4 group; and (b) no subject in the sham group, 1 (1.7%) subject in the sham+VTE PRN group (Week 44) and 2 (0.5%) subjects in the VTE2Q4+PRN group (Week 32 and Week 40) from Week 24 to Week 52.

A post dose absolute IOP value of ≥35 mmHg was reported: (a) from week to Week 24 in the sham group in 2 subjects at Week 12 and in the combined VTE2Q4 group for 2 subjects after the first injection and for 1 subject each at Weeks 8 and 16; and (b) from Week 24 to Week 52 in no subjects in the sham group, 2 (3.3%) subjects in the sham+VTE PRN group (Week 40 and Week 44), and 1 (0.5%) subject in the VTE2Q4+PRN group (Week 36).

In both treatment groups, mean post-dose IOP was increased relative to mean pre-dose IOP throughout the studies. In Weeks 0 to 24, the change from pre dose to post dose IOP was greater in the combined VTE2Q4 group (2.2 to 2.9 mmHg) than in the combined sham group (0.1 to 0.9 mmHg). In Weeks 0-52, the change from pre-dose to post dose IOP ranged from -0.3 to 1.4 mmHg in the sham group, 1.2 to 2.9 mmHg in the sham+VTE PRN group and 0.9 to 2.1 mmHg in the VTE2Q4+PRN group.

7.5.3. Immunogenicity

In COPERNICUS, samples from 188 subjects were collected at screening, pre-dose at Weeks 12, 24 and 52, and at early termination and evaluated for anti-drug antibodies (ADA). A total of 8/188 (4.3%) subjects were ADA positive; 3/74 (4.1%) in the sham+VTE PRN group and 5/114 (4.4%) in the VTE2Q4+PRN group. In the sham+VTE PRN group, all 3 ADA positive subjects were positive at baseline and in subsequent samples with no titres exceeding 30 but no subjects showed treatment-emergent reactivity. In the VTE2Q4+PRN group, of the 5 ADA positive subjects, 2 were ADA positive at baseline (1 at baseline only with a titre of 30 and 1 at baseline and in subsequent samples with no titres exceeding 30). The other 3 ADA positive subjects in the VTE2Q4+PRN group were all negative at baseline and positive at Week 52. These 3 subjects (2.6%) appeared to demonstrate a treatment-emergent positive ADA response but the titres were low with no titre exceeding the minimum of 30. None of the ADA positive subjects tested positive for neutralizing antibodies. No effects of ADA on safety or efficacy at Week 52 were observed but the number of ADA subjects is too small for meaningful conclusions to be drawn.

In GALILEO, samples from 172 patients were collected at screening, pre-dose at Weeks 12, 24 and 52, and at early termination and evaluated for ADA. A total of 9/172 (5.2%) subjects were ADA positive at any time-point: 5/68 (7.6%) subjects in the sham+VTE PRN group (titre levels low at 30) and 4/104 (3.8%) subjects in the VTE2Q4+PRN group (titre levels 30 to 120). However, all 5 subjects in the sham+VTE group tested ADA positive prior to Week 52 (that is, prior to the administration of VTE). The results in the sham group appear to be due to pre-existing immunoreactivity and not due to an ADA response to VTE. Of the 4 ADA positive subjects in the VTE2Q4+PRN group, 3 (2.9%) were negative pre dose and became positive post dose (that is, treatment emergent positive ADA). The remaining ADA positive subject in the VTE2Q4+PRN group was positive pre dose (titre of 30) but negative post-dose. No effects of ADA on safety or efficacy at Week 52 were observed but the number of ADA subjects is too small for meaningful conclusions to be drawn.

7.5.4. Safety in special populations

7.5.4.1. Weeks 0 to 24 (integrated analysis)

The overall safety profiles of the special populations treated with VTE2Q4 examined in the integrated analysis of safety for the most important adverse event categories identified in the total population are briefly commented on below.

Sex: Overall, there were no marked differences in the safely profiles of males (n=128) and females (n=90) treated with VTE2Q4.

Age: The integrated safety analysis provided a comparison of the safety profiles of subjects aged < 65 years (n=106), ≥ 65 to < 75 years (n=74), and ≥ 75 years (n=38). There was a trend for TEAEs (any) associated with treatment with VTE2Q4 to increase with age and a trend for ocular TEAEs (any) in the study eye to occur more frequently in the oldest age group.

Race: Overall, the safety profile of the White group (n=163) treated with VTE2Q4 was inferior to that of Asians, (n=33). However, the marked imbalance in subject numbers between the two groups precludes meaningful pair-wise comparisons.

Renal impairment: Overall, there were no marked differences in the safety profiles of subjects with normal renal function (n=118) and subjects with mild renal impairment (n=75) treated with VTE2Q4 during the first 24 weeks of treatment. Subjects with moderate and severe renal impairments were pooled (n=23) because of the small number of subjects with severe renal impairment. TEAEs (any) and SAEs (any) occurred more commonly in the moderate/severe renal impairment group compared with subjects with normal renal function and mild renal impairment. However, the number of subjects in the moderate/severe renal impairment group was notably smaller than the number of subjects in the two other groups. There were no

marked differences across the three groups as regards ocular TEAEs (any) and injection-related TEAEs (any) in the study eye.

Diabetes mellitus: Overall, there were no marked differences in the safety profiles of subjects with (n=47) or without (n=171) a history of diabetes mellitus treated with VTE2Q4.

Cataracts: Overall, the safety profile of subjects with cataracts (n=121) treated with VTE2Q4 was inferior to that of subjects without (n=97) cataracts.

Hypertension: Overall, there were no marked differences in the safety profiles of subjects with (n=120) or without (n=98) a history of hypertension treated with VTE2Q4.

CVA/stroke: There was a notably higher incidence of injection-related TEAEs (any) in subjects with a history of stroke/CVA (n=13) than in subjects without a history of stroke/CVA (n=205). However, there was a marked imbalance in subject numbers between the two groups which precludes meaningful pair wise comparisons.

Myocardial infarction: There was a notably higher incidence of SAEs (any) in subjects with a history of MI (n=20) than in subjects without a history of stroke/CVA (n=198). However, there was a marked imbalance in subject numbers between the two groups which precludes meaningful pair wise comparisons.

7.5.4.2. Week 24 to 52, Week 24 completers (integrated analysis)

The overall safety profiles of the special populations treated with VTE2Q4 examined in the integrated analysis of safety for the most important adverse event categories identified in the total population are briefly commented on below.

Sex: Overall, there were no marked differences in the safely profiles of males (n=120) or females (n=87) treated with VTE2Q4+PRN.

Age: Overall, the was no marked difference in the safety profiles of subjects aged < 65 years (n=100), ≥ 65 to < 75 years (n=70), or ≥ 75 years (n=37) treated with VTE2Q4+PRN.

Race: The incidence of TEAEs (any), ocular TEAEs (any) study eye, and injection-related TEAEs (any) study eye were notably higher in subjects in the White group (n=155) than in the Asian (group) treated with VTE2Q4+PRN. However, the marked imbalance in subject numbers between the two groups precludes meaningful pair-wise comparisons.

Renal impairment: Overall, there was no marked difference in the safety profiles of subjects with normal renal function (n=111), mild renal impairment (n=72) or moderate/severe renal impairment (n=22).

Diabetes mellitus: Overall, there were no marked differences in the safety profiles of subjects with (n=46) or without (n=161) a history of diabetes mellitus treated with VTE2Q4+PRN.

Cataracts: There was a notably increased incidence of injection-related TEAEs (any) in the study eye in subjects with a history of cataracts (n=96) compared with subjects without a history of cataracts (n=96) treated with VTE2Q4+PRN. There were no other noteworthy differences between the safety profiles of the two groups.

Hypertension: There was a notably increased incidence of TEAEs (any) in subjects with a history of hypertension (n=113) than in subjects without a history of hypertension (n=94) treated with VTE2Q4+PRN. There were no other noteworthy differences between the safety profiles of the two groups.

CVA/stroke: The marked imbalance in subject numbers between the two groups precludes meaningful pair-wise comparisons (that is, with [n=13] and without [n=194] a history of stroke).

Myocardial infarction: The marked imbalance in subject numbers between the two groups precludes meaningful pair-wise comparisons (that is, with [n=18] and without [n=155] a history of MI).

7.6. Long-term safety

7.6.1. COPERNICUS – Week 100 results

7.6.1.1. Exposure

The data through Week 100 were collected according to the original protocol dated 18 May 2009, and 1 subsequent protocol amendment 1 dated 04 January 2010. The CSR (Week 100) included results based on the data obtained from 08 July 2009 (first subject's first visit) to 04 April 2012 (last subject's end of study visit). The safety data described in the following summary relates to the safety analysis set unless otherwise stated.

Starting at Week 52, all subjects were eligible to continue in a 1 year PRN extension and evaluated every 12 weeks to determine eligibility to receive open-label VTE 2 mg IVT injections according to pre-specified re treatment criteria. However, if in the investigator's opinion more frequent dosing than every 12 weeks was required then dosing may have occurred as frequently as every 4 weeks. Week 88 was the last mandatory study visit when a PRN injection could be administered but as investigators were allowed to bring in subjects as often as monthly for PRN injections the last possible PRN injection was at Week 96.

The VTE2Q4+PRN group received over 3 times as many VTE injections over the duration of the study compared to the sham+VTE PRN group (total number of injections 1293 versus 384). From Weeks 24 to 100, the mean time to the first VTE injection was shorter in the sham+VTE PRN group (54.5 days) than in the VTE2Q4+PRN group (92.8 days). In the sham+VTE PRN group, the time to first injection in Weeks 24 to 100 was 4 weeks for most subjects (80.0%), followed by 8 weeks for 10.0% of subjects. In the VTE2Q4+PRN group, the time to the first injection was evenly divided between 4 weeks (29.1%), 8 weeks (17.3%), 12 weeks (24.5%), and >12 weeks (24.5%). In the sham+VTE PRN group, 85.0% (51/60) of subjects received re treatment at least once in a 4 week interval and the corresponding figure in the VTE2Q4+PRN group was 70.0% (77/110). The mean time between VTE injections was shorter in the sham+VTE PRN group (61.40 days) than in the VTE2Q4+PRN group (87.41 days).

7.6.1.2. Adverse events

7.6.1.2.1. Overview of adverse events

Over the 100 weeks of the study, nearly all subjects in the sham+VTE PRN group and the VTE2Q4+PRN group experienced at least 1 TEAE (70/74 [94.6%] versus 112/114 [98.2%], respectively).

7.6.1.2.2. Ocular TEAEs in the study eye

The incidence of ocular TEAEs in the study eye was similar in subjects in both treatment groups (63/74 [85.1%], sham+VTE PRN versus 100/114 [87.7%], VTE2Q4+PRN]). The most commonly reported ocular TEAEs occurring in ≥ 10% of subjects in both treatment groups (sham+VTE PRN versus VTE2Q4+PRN) were: visual acuity reduced (27.0% versus 28.1%); conjunctival haemorrhage (20.3% versus 19.3%); retinal haemorrhage (16.2% versus 15.8%); and IOP increased (17.6% versus 12.3%).

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 (respectively): 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%).

The majority of ocular TEAEs in the study eye in subjects in both treatment groups were mild or moderate in intensity (52 [70.2%], sham+VTE PRN versus 81 [78.1%], VTE2Q4+PRN). The most commonly reported severe ocular TEAEs in the study eye were (sham+VTE PRN versus VTE2Q4+PRN): visual acuity reduced (2 [2.7%] versus 2 [1.8%]); macular oedema (1 [1.4%] versus 2 [1.8%]); glaucoma (2 [2.7%] versus 0 [0%]); vitreous haemorrhage (2 [2.7%] versus 0 [0%]); and cataract (1 [1.4%] versus 1 [0.9%]). All other severe ocular TEAEs in the study eye occurred in no more than 1 subject in either treatment group.

Comment: The incidence of ocular TEAEs in subjects in the study eye from baseline to Week 100 was similar in the sham+VTE PRN and the VTE2Q4+VTE groups (85.1% versus 87.7%, respectively). 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 group (3 [4.1%]), and the similar proportion of patients with visual reduced (20.7% versus 28.1%, respectively). Other complications of CRVO, including cystoid macular oedema and retinal exudates, occurred more frequently in subjects in the VTE2Q4+PRN group than in the sham+VTE PRN group, while vitreous haemorrhage and retinal pigment epitheliopathy occurred more frequently in the sham+VTE PRN group than in the VTE2Q4+PRN group.

7.6.1.2.3. Ocular TEAEs in the fellow eye

From baseline to Week 100, the overall incidence of ocular TEAEs in the fellow eye was lower in subjects in the sham+VTE PRN group than in the VTE2Q4+PRN group (34/74 [45.9%] versus 60/114 [52.6%], respectively). The most frequently occurring ocular TEAEs in the fellow eye occurring in ≥ 3% of subjects in either treatment group were (sham+VTE PRN versus VTE2Q4+PRN): IOP increased (8.1% versus 9.6%); retinal haemorrhage (6.8% versus 7.0%); cataract (4.1% versus 6.1%); dry eye (8.1% versus 2,6%); visual acuity reduced (1.4% versus 4.4%); vitreous detachment (3.5% versus 2.7%); retinal degeneration (4.1% versus 1.8%); cataract nuclear (0% versus 3.5%); diabetic retinopathy (4.1% versus 0.9%); posterior capsule opacification (0% versus 3.5%); retinal vein occlusion (0 versus 3.5%), and punctate keratitis (4.1% versus 0%).

7.6.1.2.4. Non-ocular TEAEs

The incidence of non-ocular TEAEs was similar in subjects in the sham+VTE PRN and VTE2Q4+PRN groups (60 [81.1%] versus 88 [77.2%]). The most commonly reported non-ocular TEAE in subjects in the VTE2Q4+PRN group (≥ 10%) versus the sham+VTE group was hypertension (19.3% versus 16.2%). No other non-ocular TEAEs were reported in ≥ 10% of subjects in the VTE2Q4+PRN group. 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 from baseline to Week 100 were: hypertension (19.3% versus 16.2%); nasopharyngitis (8.8% versus 6.8%); upper respiratory tract infections (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%). The majority of non-ocular TEAEs were mild or moderate in intensity in subjects in both treatment groups. Severe non-ocular TEAEs occurred in a greater proportion of subjects in the sham+VTE PRN group (13 [17.6%]) than in the VTE2Q4+PRN group (13 [11.4%]). Severe bronchitis and severe pneumonia were each experienced by 2 subjects in the sham+VTE PRN group. None of the other severe non-ocular TEAEs occurred in more than 1 subject in either treatment group.

7.6.1.2.5. Drug-related TEAEs

The overall incidence of drug-related ocular TEAEs in the study eye from baseline to Week 100 was low (5 subjects [6.8%], sham+VTE PRN versus 3 subjects [2.6%], VTE2Q4+PRN). No drug-related ocular TEAEs in the study eye occurred in more than 1 subject in either treatment group. Drug-related non-ocular TEAEs from baseline to Week 100 were reported in 1 subject in

the sham+VTE PRN group (acute MI) and 1 subject in the VTE2Q4+PRN group (urine protein/creatine ratio increased.

7.6.1.2.6. Injection-related TEAEs

The incidence of injection-related TEAEs in the study eye was higher in subjects in the sham+VTE PRN group (21/74 [28.4%]) than in the VTE2Q4+PRN group (45/114 [39.5%]). The most commonly reported injection-related TEAEs occurring with an incidence of ≥ 5% of subjects in either of the two groups (sham+VTE PRN versus VTE2Q4+PRN) were conjunctival haemorrhage (18.9% versus 18.4%) and eye pain (5.4% versus 13.2%). Other 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: 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. From baseline to Week 100, there was 1 injection related TEAE reported in the **fellow eye** (conjunctival haemorrhage) in the VTE2Q4+PRN group.

7.6.1.3. Death and other treatment emergent serious adverse events (SAEs)

7.6.1.3.1. Death

There were 4 deaths from Week 0 to Week 100 and all occurred in the sham+VTE PRN group (1 arrhythmia 54 days after last dose; 1 acute MI 3 days after last dose; 1 oesophageal adenocarcinoma stage IV, 85 days after last dose; 1 pneumonia 47 days after last dose).

7.6.1.3.2. Ocular treatment-emergent serious adverse events (SAEs)

Ocular SAEs in the **study eye** reported in subjects from baseline to Week 100 are summarised below in Table 31. Overall, the incidence of ocular SAEs in the study eye was about 2 fold higher in the sham+VTE PRN group (16.2%) than in the VTE2Q4+PRN group (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%]). All other ocular SAEs in the study eye in the VTE2Q4+PRN group were each reported in 1 subject and with the same or lower incidence than in the sham+VTE PRN group.

Table 31: COPERNICUS – Baseline to Week 100, ocular SAEs in the study eye; SAF.

Preferred Term MedDRA Version 15.0	Sham+PRN (N=74)	VEGF Trap-Eye 2Q4+PRN (N=114)	Total (N=188)
Number of subjects with at least 1 ocular SAE in study eye, n (%)	12 (16.2%)	10 (8.8%)	22 (11.7%)
Vitreous haemorrhage	5 (6.8%)	1 (0.9%)	6 (3.2%)
Cataract	1 (1.4%)	4 (3.5%)	5 (2.7%)
Glaucoma	3 (4.1%)	0	3 (1.6%)
Cystoid macular oedema	0	2 (1.8%)	2 (1.1%)
Iris neovascularisation	2 (2.7%)	0	2 (1.1%)
Retinal haemorrhage	2 (2.7%)	0	2 (1.1%)
Retinal tear	2 (2.7%)	0	2 (1.1%)
Retinal vein occlusion	1 (1.4%)	1 (0.9%)	2 (1.1%)
Visual acuity reduced	1 (1.4%)	1 (0.9%)	2 (1.1%)
Corneal abrasion	0	1 (0.9%)	1 (0.5%)
Endophthalmitis	0	1 (0.9%)	1 (0.5%)
Macular oedema	0	1 (0.9%)	1 (0.5%)
Retinal artery occlusion	0	1 (0.9%)	1 (0.5%)
Retinal vascular disorder	0	1 (0.9%)	1 (0.5%)

From baseline to Week 100, ocular treatment-emergent SAEs in the **fellow eye** were experienced by 2 subjects in the VTE2Q4+PRN group (cataract, conjunctival haemorrhage, facial bones fracture, IOP increased, macular fibrosis, posterior capsule opacification, and vitreous haemorrhage), and 1 subject in the sham+VTE PRN group (periorbital cellulitis)

7.6.1.3.3. Treatment emergent non-ocular serious adverse events (SAEs)

From baseline to Week 100, the incidence of non-ocular SAEs was higher in subjects in the sham+VTE group (19/74 [25.7%]) than in the VTE2Q4+PRN group (24/114 [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%]). Non-ocular SAEs reported ≥ 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%]); renal failure acute (2 [2.7%] versus 1 [0.9%]). All other non-ocular SAEs occurred in no more than 1 subject in either treatment group.

7.6.1.3.4. Drug-related serious adverse events (SAEs)

From baseline to Week 100, 1 subject in each treatment group experienced 1 drug-related ocular SAE in the study eye (cataract, sham+VTE PRN; retinal artery occlusion, VTE2Q4+PRN). There were no drug-related ocular SAEs in the fellow eye. There was 1 subject in the sham+VTE PRN group with a drug-related non-ocular SAE (acute MI).

7.6.1.3.5. Injection-related serious adverse events (SAEs)

From baseline to Week 100, 2 subjects in the VTE2Q4+PRN group each experienced 1 injection-related SAE in the study eye: 1 endophthalmitis; 1 cataract. There were no other injection-related SAEs in either treatment group.

7.6.1.4. TEAEs leading to discontinuation of the study drug

The incidence of ocular and non-ocular TEAEs leading to discontinuation of the study drug was higher in subjects in the sham+VTE group (5 [6.8%]; all ocular TEAEs) than in the VTE2Q4+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 2 non-ocular TEAEs leading to discontinuation of the study drug in the VTE2Q4+PRN group were metastatic renal cell carcinoma (1 [0.9%] VTE2Q4+PRN versus 0 [0%] sham+VTE PRN), and non-small cell lung cancer (1 [0.9%] VTE2Q4+PRN versus 0 [0%] sham+VTE PRN).

7.6.1.5. TEAEs and SAEs of interest

7.6.1.5.1. Ocular TEAEs and SAEs of interest in the study eye

The proportion of subjects with at least one TEAE of interest (ocular and non-ocular) from baseline to Week 100 was 67.6% (50/74) in the sham+VTE PRN group and 63.2% (72/114) in the VT2Q4+PRN group. The incidence of subjects who experienced at least one ocular TEAE of interest in the study eye was similar in the sham+VTE PRN (39/74 [52.7%]) and VTE2Q4+PRN (58/114 [50.9%]) groups. Ocular TEAEs of interest occurring in ≥ 10% of all subjects were (sham+VTE PRN versus VTE2Q4+PRN): visual acuity reduced (20 [27.0%] versus 32 [28.1%]); conjunctival haemorrhage (13 [17.6%] versus 19 [16.7%]); and eye pain (4 [5.4%] versus 15 [13.2%]). Ocular TEAEs of interest in study eye reported in ≥ 2% more subjects in the VTE2Q4+PRN group than in the sham+VTE PRN group were: eye pain (15 [13.2%] versus 4 [5.4%]); vitreous floaters (5 [4.4%] versus 1 [1.4%]); and IOP increased (3 [2.6%] versus 0 [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 1 SAE was visual acuity reduced, and in the VTE2Q4+PRN group the 2 SAEs were visual acuity reduced and endophthalmitis.

7.6.1.5.2. Non-ocular TEAEs and SAEs of interest

The proportion of subjects with at least one TEAE of interest (ocular and non-ocular) from baseline to Week 100 was 67.6% (50/74) in the sham+VTE PRN group and 63.2% (72/114) in the VTE2Q4+PRN group. The incidence of subjects who experienced at least one non-ocular TEAE of interest was higher in subjects in the sham+VTE PRN group (23/74 [31.1%]) than in the VTE2Q4+PRN group (29/114 [25.4%]). The only non-ocular TEAE of interest with an incidence of ≥ 10% in either group was hypertension (12 [16.2%], sham+VTE PRN versus 22 [19.3%], VTE2Q4+PRN). No other non-ocular TEAEs of interest were reported in ≥ 2% more subjects in the VTE2Q4+PRN than in the sham+VTE PRN group. The overall incidence of subjects who experienced at least one ocular SAE of interest was low in both treatment groups (2 [2.7%] sham+VTE PRN versus 3 [2.6%] VTE2Q4+PRN). In the sham+VTE PRN group the non-ocular SAE events of interest in the 2 subjects were acute MI (1 subject) and carotid artery stenosis (1 subject) and in the VTE2Q4+PRN group the 3 subjects reported 4 events consisting of haemorrhagic cerebral infarction, MI, subarachnoid haemorrhage and epistaxis.

7.6.1.5.3. Arterial thromboembolic events (ATEs) of interest, APTC events

During the 100 weeks of treatment, 4 subjects (2/74 [2.7%], sham+VTE PRN; 2/114 [1.8%], VTE2Q4+PRN) experienced ATE/APTC events. Two (2) subjects in the sham+VTE PRN 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).

7.6.1.6. Laboratory tests

7.6.1.6.1. Haematology

No trends towards an increase or decrease in mean values from baseline to Week 100 were seen in haematology parameters in either of the two treatment groups. Few subjects had shifts from “normal” at baseline to either “high” or “low” at subsequent visits, and the observed shifts were within the range of variability expected for this population. Overall, the observed differences in the proportion of subjects in the two treatment groups with haematology values above the upper limit of normal or below the lower limit of normal are unlikely to be clinically significant.

During the 100 weeks of treatment, pre-defined haematology laboratory abnormalities were observed in a small number of subjects with a similar frequency in both treatment groups for most abnormalities. The exceptions (≥ 2% difference in subjects between treatment groups) were absolute eosinophils increased more common in the VTE2Q4+PRN treatment group than in the sham+VTE PRN group (7/104 [6.7%] versus 2/65 [3.1%]), absolute monocytes increased more common in the sham+VTE PRN group than in the VTE2Q4+PRN group (11/65 [16.9%] versus 10/103 [9.7%]), and platelet count decreased more common in the sham+VTE PRN group than in the VTE2Q4+PRN group (2/65 [3.1%] versus 1/101 [1.0%]).

7.6.1.6.2. Clinical chemistry

No trends towards an increase or decrease in mean values from baseline to Week 100 were seen in clinical chemistry parameters in either of the two treatment groups. Few subjects had shifts from “normal” at baseline to either “high” or “low” at subsequent visits and the observed shifts were within the range of variability expected for this population. Overall, the observed differences in the proportion of subjects in the two treatment groups with clinical chemistry values above the upper limit of normal or below the lower limit of normal are unlikely to be clinically significant.

During the 100 weeks of treatment, pre-defined clinical chemistry abnormalities were observed in a small number of subjects with a similar frequency in both treatment groups for most abnormalities. The exceptions (≥ 2% difference in subjects between treatment groups) were: alkaline phosphatase increased more common in the sham+VTE PRN group than in the VTE2Q4+PRN group (2/68 [2.9%] versus 1/110 [0.9%]); creatinine increased (absolute) more common in the VTE2Q4+PRN group than in the sham+VTE PRN group (7/104 [6.7%] versus 2/65 [3.1%]); creatinine increased ≥ 30% from baseline more common in the VTE2Q4+PRN group than in the sham+VTE PRN group (13/104 [12.5%] versus 4/65 [6.2%]); hypoglycaemia more common in the VTE2Q4+PRN than in the sham+VTE PRN group (13/100 [13.0%] versus 3/65 [4.6%]); and sodium decreased more common in VTE2Q4+PRN group than in the sham+VTE PRN group (3/100 [2.7%] versus 0% [0/68]). Of note, alanine aminotransferase (ALT) > 3 x ULN and aspartate aminotransferase (AST) > 3 x ULN were each reported in 1/100 subjects (1.0%) in the VTE2Q4+PRN group and 0/68 subjects (0%) in the sham+VTE group.

7.6.1.6.3. Urinalysis

No trends towards an increase or decrease in mean values over time were seen in the urinalysis parameters tested in either of the two treatment groups at Week 100. Overall, urinalysis testing was normal (negative) for most subjects at baseline and at Week 100. Shifts from normal at baseline to either high or low (range from trace to +++) at Week 100 were few, with a similar incidence of shifts from normal to high, as from normal to low in both treatment groups. No urinalysis results meeting pre-defined criteria were reported at any time during the study.

7.6.1.6.4. Intraocular pressure and vital signs

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+PRN group: (a) ≥ 10 mmHg from baseline to pre-dose, 13.5% [10/74] versus 7.0% [8/114]; (b) absolute value of ≥ 21 mmHg pre-dose, 31.1% [23/74] versus 26.3% [30/114]; and (c) absolute value ≥ 35 mmHg at any time, 6.8% [5/74] versus 1.8% [2/114]. Mean blood pressure, temperature and pulse were similar between treatment groups at baseline, and fluctuations throughout the study in both treatment groups were considered to be not clinically meaningful.

7.6.1.7. Ophthalmic examination

The results of pre specified ophthalmic from baseline to Week 100 did not notably differ from those described previously for baseline to Week 52. In general, there were no clinically significant differences between the two treatment groups.

7.6.2. GALILEO – Week 76 results

7.6.2.1. Exposure

The data collected from baseline through to Week 76 and presented in the final CSR (Week 76), dated 08 October 2012 were collected according to the original protocol dated 19 June 2009, protocol amendment 1 dated 11 September 2009 (Japan only), protocol amendment 2 dated 02 December 2009 (France only) and protocol amendment 3 dated 30 June 2012. The CSR (Week 76) included data collected from the first subject first visit (28 October 2009) to the last subject last visit (01 February 2012). The safety data described in the following summary relates to the safety analysis set unless otherwise stated.

Subjects in the VTE2Q4+PRN treatment group received VTE2Q4 from Day 1 through Week 20. VTE was then given PRN from Week 24 through to Week 68 in accordance with pre-specified re treatment criteria. Up to Week 52, subjects were evaluated every 4 weeks and every 8 weeks after Week 52. If re treatment criteria were not met at a given visit from Week 24 to week 68, subjects received a sham injection in order to maintain masking. No treatment was administered at the end of study visit/Week 76.

Subjects in the sham group received sham injections every 4 weeks from day 1 through Week 20. Sham treatment was then continued monthly from Week 24 through to Week 48. At Week 52, subjects in the sham group received VTE unless the masked investigator decided for medical reasons that treatment with active drug was not in the best interest of the subject. If VTE was not administered at Week 52, the subject received sham treatment. After that, subjects returned every 8 weeks (that is, at Week 60 and Week 68) and received VTE if the pre specified re treatment criteria were met, or sham injection if the criteria were not met in order to maintain masking. No treatment was administered at the end of study visit/Week 76.

During the 76 weeks of treatment, total exposure to VTE in the VTE2Q4+PRN group was 18.3 mg over a mean duration of 450 days and in the sham+VTE PRN group total exposure to VTE was 2.5 mg over a mean duration of 400 days. The mean number of injections administered (active and sham) was higher in the VTE2Q4+PRN group (14.3) than in the sham+VTE PRN group (12.7).

In the 91 subjects in the VTE2Q4+PRN group who completed Week 52, the mean (SD) number of VTE injections from Week 52 to Week 76 was 1.3 (1.1) and in the 52 subjects in the sham+VTE PRN group who completed 52 weeks of treatment the corresponding figure was 1.7 (1.1) injections. Of the 91 subjects in the VTE2Q4+PRN group who completed Week 52, 64 (69.2%) received 1 to 3 VTE injections from Week 52 to Week 76 and 30.8% received no VTE injections during this period. In the 52 subjects in the sham+VTE PRN group who completed Week 52, 42 (80.8%) received 1 to 3 VTE injections from Week 52 to Week 76 and 19.2% received no VTE injection during this period.

7.6.2.2. Adverse events

7.6.2.2.1. Overview of adverse events

Over the 76 weeks of the study the majority of subjects in both the sham+VTE PRN and VTE2Q4+PRN groups experienced at least 1 TEAE (61/68 [89.7%] versus 91/104 [87.5%], respectively).

7.6.2.2.2. Ocular TEAEs in the study eye

The incidence of ocular TEAEs in subjects in the study eye from baseline to Week 76 was similar in the sham+VTE PRN and the VTE2Q4+PRN groups (75.0% [51/68] versus 78.8% [82/104], respectively). The most commonly reported ocular TEAEs occurring in ≥ 10% of subjects in both treatment groups were (sham+VTE PRN versus VTE2Q4+PRN): macular oedema (25.0% versus 39.4%); retinal haemorrhage (11.8% versus 15.4%); visual acuity reduced (13.2% versus 14.4%); retinal vascular disorder (11.8% versus 11.5%); and macular ischaemia (10.3% versus 10.6%). 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 (respectively): 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%).

The majority of ocular TEAEs in the study eye in subjects in both treatment groups were mild or moderate in intensity (46/68 [67.6%], sham+VTE PRN versus 72/104 [69.2%], VTE2Q4+PRN). Overall, the number of subjects with severe ocular TEAEs in the study eye was low (15 subjects; 8.7%). The only severe ocular TEAE in the study eye reported in both treatment groups was macular oedema (1.5%, sham+VTE PRN versus 1.9%, VTE2Q4+PRN). No subject in the sham+VTE PRN group experienced a severe ocular TEAE in the study eye after initiation of VTE treatment. Severe visual acuity reductions in subjects in the VTE2Q4+PRN group were all reported after the switch to PRN dosing and before Week 52 (3 [2.9%], VTE2Q4+PRN versus 0 [0%], sham+VTE PRN).

Comment: 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). Other complications of CRVO including 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.

7.6.2.2.3. Ocular TEAEs in the fellow eye

From baseline to Week 76, the overall incidence of ocular TEAEs in the fellow eye was similar in subjects in the sham+VTE PRN and VTE2Q4+PRN groups (16/68 [23.5%] versus 23/104 [22.1%], respectively). No ocular TEAEs in the fellow eye occurring in ≥ 3% of subjects were reported in either of the two treatment groups. The most commonly occurring ocular TEAEs in the fellow eye occurring in the two treatment groups were (sham+VTE PRN versus VTE2Q4+PRN): cataract (2.9% versus 2.9%); retinal haemorrhage (2.9% versus 2.9%); dry eye (1.5% versus 2.9%); and vitreous detachment (0% versus 2.9%). All other ocular TEAEs in the fellow eye occurred each occurred in 1 subject only in the sham+VTE PRN group and ≤ 2 subjects in the VTE2Q4+PRN group.

7.6.2.2.4. Non-ocular TEAEs

The proportion of subjects experiencing a non-ocular TEAE was higher 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 or sham+VTE groups 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%). The majority of non-ocular TEAEs were mild or moderate in intensity in subjects in both treatment groups. Non-ocular TEAEs classified as severe in intensity were reported in 7 subjects (10.3%) in the sham+VTE PRN group and 6 subjects (5.8%) in the VTE2Q4+PRN group. No severe non-ocular TEAEs were reported in more than 1 subject in the VTE2Q4+PRN group, while the only severe non-ocular TEAE reported in more than 1 subject in the sham+VTE PRN group was syncope (2 [2.9%]).

7.6.2.2.5. Drug-related TEAEs

From baseline to Week 76, drug-related ocular TEAEs in the study eye were reported in 7.4% (5/68) of subjects in the sham+VTE PRN group and 9.6% (10/104) of subjects in the VTE2Q4+PRN group. The most commonly reported drug-related ocular TEAEs in the study eye were IOP increased in subjects in the VTE2Q4+PRN group (4.8%, VTE2Q4+PRN versus 1.5%, sham+VTE PRN) and eye irritation in the sham+VTE PRN group (2.9%, sham+VTE PRN versus 1.9%, VTE2Q4+PRN). No other drug-related ocular TEAEs occurred in ≥ 2% of subjects in either treatment group. One (1) subject in the sham+VTE PRN group experienced a drug-related ocular TEAE in the fellow eye (IOP increased reported prior to the initiation of active treatment). No drug-related non-ocular TEAEs were reported in either treatment group.

7.6.2.2.6. Injection-related TEAEs in the study eye and fellow eye

The incidence of injection-related TEAEs in the study eye was higher in subjects in the VTE2Q4+PRN group (44/104 [42.3%]) than in the sham+VTE PRN group (27/68 [39.7%]). The most commonly reported injection-related TEAEs occurring with an incidence of ≥ 5% of subjects in either of the two groups were (sham+VTE PRN versus VTE2Q4+PRN): conjunctival haemorrhage (7.4% versus 17.3%); eye pain (5.9% versus 13.5%); eye irritation (10.3% versus 5.8%); ocular hyperaemia (5.9% versus 5.8%); foreign body sensation in eyes (4.4% versus 6.7%); lacrimation increased (7.4% versus 3.8%); and IOP increased (4.4% versus 12.5%). 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: 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%). One (1) subject in the sham+VTE PRN group was reported to have an injection-related TEAE in the fellow eye of eyelid function disorder (reported before the initiation of active treatment), although it is unclear why the fellow eye would experience an injection-related TEAE. No injection-related non-ocular TEAEs were reported in either treatment group.

7.6.2.3. Death and other treatment emergent serious adverse events (SAEs)

7.6.2.3.1. Death

No deaths occurred from baseline through to Week 76.

7.6.2.3.2. Ocular treatment-emergent SAEs

Ocular SAEs in the **study eye** are summarised below in Table 32. The proportion of subjects with ocular SAEs in the study eye was higher 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 ≥ 2% of subjects in either treatment group were macular oedema in the VTE2Q4+PRN group (3.8%, VTE2Q4+PRN versus 2.9%, sham+VTE PRN), and glaucoma in the sham+VTE PRN group (2.9%, sham+VTE PRN versus 0%, VTE2Q4+PRN).

Table 32: GALILEO – Week 0 to Week 76, treatment-emergent SAEs in the study eye; SAF.

System Organ Class MedDRA PT	Sham+VTE PRN N=68 n (%)	VTE2Q4+PRN N=104 n (%)	Total N=172 n (%)
Any Ocular SAE (study eye)	**6 (8.8)**	**11 (10.6)**	**17 (9.9)**
Eye Disorders	**6 (8.8)**	**11 (10.6)**	**17 (9.9)**
Macular oedema	2 (2.9)	4 (3.8)	6 (3.5)
Visual acuity reduced	1 (1.5)	2 (1.9)	3 (1.7)
Glaucoma	2 (2.9)	0	2 (1.2)
Vitreous hemorrhage	1 (1.5)	1 (1.0)	2 (1.2)
Blindness unilateral	0	1 (1.0)	1 (0.6)
Iris neovascularisation	0	1 (1.0)	1 (0.6)
Macular fibrosis	0	1 (1.0)	1 (0.6)
Macular ischaemia	0	1 (1.0)	1 (0.6)
Retinal vein occlusion	0	1 (1.0)	1 (0.6)
Vitreous detachment	0	1 (1.0)	1 (0.6)

Ocular SAEs in the **fellow eye** were reported in only 1 subject (1.5%) in the sham+VTE PRN group (increased IOP after initiation of active treatment).

7.6.2.3.3. Non-ocular treatment-emergent SAEs

From baseline to Week 76, the incidence of non-ocular SAEs was higher in subjects in the sham+VTE PRN 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%]).

7.6.2.3.4. Drug-related SAEs

From baseline to Week 76, drug-related SAEs were reported in 1 (1.5%) subject in the sham+VTE PRN group (renal failure prior to Week 24), and 2 (1.9%) subjects in the VTE2Q4+PRN group (1 macular ischaemia prior to Week 24; 1 hepatic function abnormal Week 24 to Week 52).

7.6.2.4. TEAEs leading to discontinuation of the study drug

The incidence TEAEs leading to discontinuation of the study drug was higher in subjects in the sham+VTE PRN group than in the VTE2Q4+PRN group (7/68 [10.3%] versus 7/104 [6.7%],

respectively). In the VTE2Q4+PRN group, the only TEAE leading to discontinuation of the study drug in more than 1 subject was iris neovascularisation (2 [1.9%], VTE2Q4+PRN versus 0 [0%], sham+VTE PRN). In the sham+VTE PRN group, the only TEAEs leading to discontinuation of the study drug in more than 1 subject were macular oedema (2 [2.9%], sham+VTE PRN versus 1 [1.0%], VTE2Q4+PRN), retinal neovascularisation (3 [4.4%], sham+VTE PRN versus 0 [1.0%], VTE2Q4+PRN), and glaucoma (2 [2.9%], sham+VTE PRN versus 0 [0%], VTE2Q4+PRN).

7.6.2.5. TEAEs and SAEs of pre-specified interest

7.6.2.5.1. Ocular events of pre-specified interest in the study and fellow eyes

The proportion of subjects with at least 1 ocular TEAE of interest in the **study eye** was similar in the VTE2Q4+PRN and sham+VTE PRN groups (45/104 [43.3%] versus 29/68 [42.6%], respectively). Ocular TEAEs of interest in the study eye reported in ≥ 10% of all subjects were (sham+VTE PRN versus VTE2Q4+PRN) 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 the **fellow eye**, there were no reported ocular TEAEs of interest.

7.6.2.5.2. Non-ocular events of pre-specified interest

The proportion of subjects with at least 1 non-ocular TEAE of interest was similar in the VTE2Q4+PRN and sham+VTE PRN groups (13/104 [12.5%] versus 8/68 [11.8%]). The most commonly reported non-ocular TEAE of interest was hypertension (9.6%, VTE2Q4+PRN versus 10.3%, sham+VTE PRN). No other non-ocular TEAEs of interest were reported in more than 1 subject in each treatment group.

7.6.2.5.3. Arterial thromboembolic events (ATEs), APTC events

No ATEs were classified as APTC events by the masked adjudication committee.

7.6.2.6. Laboratory tests

7.6.2.6.1. Haematology

Haematology parameters were assessed at Weeks 12, 24, 36, 52, and 76. Overall, no clinically significant changes in mean/median values within or between treatment groups were observed, and there were no clinically meaningful shifts in values over the course of the study. The observed differences in both high and low treatment emergent laboratory haematology abnormalities over the 76 weeks of the study are considered to be unlikely to be clinically significant.

During the 76 weeks of treatment, pre-defined potentially clinically relevant haematology laboratory abnormalities were generally observed in < 5% of subjects in both treatment groups and there were no marked differences between the groups. The pre-defined haematology parameters with a ≥ 2% difference in incidence between subjects in the two treatment groups were (sham+VTE PRN versus VTE2Q4+PRN): low haematocrit (10.3% versus 2.1%); haemoglobin concentration decrease from baseline ≤ 20 g/L (11.7% versus 5.2%); high monocytes (14.3% versus 4.5%); and low WBC (3.4% versus 1.1%). There were no pre-defined haematology test abnormalities in ≥ 2% more subjects in the VTE2Q4+PRN group than in the sham+VTE PRN group.

7.6.2.6.2. Clinical chemistry

Clinical chemistry parameters were assessed at Weeks 12, 24, 36, 52, and 76. Overall, no clinically significant changes in mean/median values within or between treatment groups were observed and there were no clinically meaningful shifts in values over the course of the study. In

addition, the observed differences in both high and low treatment-emergent clinical chemistry abnormalities over the 76 weeks of the study are considered to be unlikely to be clinically significant.

During the 76 weeks of treatment, pre-defined potentially clinically relevant clinical chemistry abnormalities were generally observed in < 5% of subjects in both treatment groups, and there were no marked differences between the groups. The pre-defined clinical chemistry parameters with a ≥ 2% difference in incidence between subjects in the two treatment groups were (sham+VTE PRN versus VTE2Q4+PRN: creatinine change from baseline ≥ 30% (14.5% versus 7.2%); hypoglycaemia (12.9% versus 3.1%); hyperglycaemia (6.7% versus 12.0%); high (3.3% versus 0%); and high creatinine (3.3% versus 0%). There were no significant differences between the sham+VTE PRN and VTE2Q4+PRN groups in liver function tests (LFTS): ALT > 3 times ULN (0% versus 1/93 [1.1%]); ALT > 3 times ULN and total bilirubin > 2 times ULN (0% versus 0%); AST ≥ 3 times ULN (0% versus 1/94 [1.1%]); bilirubin ≥ 1.5 times ULN (2/62 [3.2%] versus 3/95 [3.2%]); and alkaline phosphatase 1.5 times ULN (1/61 [1.6%] versus 0%). Overall, 3 subjects in the VTE2Q4+PRNN group with normal AST and/or ALT levels at baseline experienced elevated levels during the study.

7.6.2.6.3. Urinalysis

Assessments were made at baseline at Weeks 12, 24, 36, 52, and 76. No trends towards an increase or decrease in mean or median protein/creatinine ratio and specific gravity values over time were seen in either treatment groups at Week 76. Shifts from normal levels at baseline to either high or low levels at Week 76 were few and were considered not to be associated with VTE treatment. High laboratory abnormalities for the creatinine/protein ratio were reported at a similar incidence in subjects in the two groups (7/4 [17.1%], sham+VTE PRN versus 12/72 [16.7%] VTE2Q4+PRN). No reports of high specific gravity values were reported for subjects in the VTE2Q4+PRN group, while the 2 reports for this event in the sham+VTE PRN group occurred before the initiation of VTE treatment. There were no treatment-emergent low laboratory abnormalities for the creatinine/protein ratio and 2 for low specific gravity (both in the VTE2Q4+PRN group).

7.6.2.6.4. Intraocular pressure and vital signs

Mean pre-injection IOP was normal at baseline in both treatment groups (14.4 mmHg, sham+VTE PRN; 15.2 mmHg, VTE2Q4+PRN). Mean pre-injection IOP increased slightly in both treatment groups during the study but remained normal at Week 76 (15.4 mmHg, sham+VTE PRN; 16.6 mmHg VTE2Q4+PRN). Both treatment groups showed only a slight increase in mean IOP post injection compared with pre injection throughout the study. Increases in IOP from pre to post injection were greater in the VTE2Q4+PRN group (up to 2.4 mm Hg [Week 8]) than in the sham+VTE PRN group (up to 1.4 mmHg [first injection and Week 52]). 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% (10/172) versus 7.4% (5/68); (b) absolute value of ≥ 21 mmHg pre-dose, 19.2% (20/104) versus 13.2% (9/68); and (c) absolute value ≥ 35 mmHg at any time, 4.8% (6/172) versus 1.4% (1/68).

Mean systolic and diastolic blood pressure, temperature and pulse were similar between treatment groups at baseline. Mean systolic and diastolic blood pressure, temperature and pulse fluctuated slightly relative to the baseline values in both treatment groups throughout the study. Electrocardiogram (ECGs) were recorded at baseline, Week 52 and Week 76. No clinically meaningful changes were noted between baseline and Week 52 or between baseline and Week 76 in QT, QTc (Bazett), QTc (Fridericia), PR duration, QRS duration, RR duration or ventricular rate in either treatment group. The proportion of subjects with abnormal ECGs at baseline, Week 52 and Week 76 (sham+VTE PRN versus VTE2Q4+PRN) were: 68.7% versus 55.9%; 71.4% versus 61.6%; and 74.0% versus 64.0%).

7.6.2.6.5. Ophthalmic examination

The results of pre-specified ophthalmic from baseline to Week 76 did not notably differ from those described previously for baseline to Week 52. In general, there were no clinically significant differences between the two treatment groups.

7.7. 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".

7.8. 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 0-100) 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.

7.8.1. 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 ATE/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 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, urinalysis) or vital signs in either the sham or the VTE2Q4 group from Week 0 to Week 24

7.8.2. 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 (vs 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 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 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 neutralizing 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.

7.8.3. 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 33 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. [information redacted].

Table 33: 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%)

[information redacted]

Table 34: Integrated Analysis – Overview of TEAEs 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
Any TEAE	112 (80.6)	73 (83.0)	51 (86.4)
Ocular TEAE (Study Eye)	86 (61.9)	67 (76.1)	40 (67.8)
Injection related	21 (15.1)	16 (18.2)	15 (25.4)
Drug related	3 (2.2)	2 (2.3)	2 (3.4)
Non-ocular TEAE	81 (58.3)	48 (54.5)	35 (59.3)
Ocular SAE (Study Eye)	6 (4.3)	4 (4.5)	3 (5.1)

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 35, below). Conjunctival haemorrhage, eye irritation and eye pain all occurred notably more commonly 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 35: 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 36. 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 36: 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 2-3 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%).

8. First round benefit-risk assessment

8.1. 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 de-stabilisation 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.

8.2. 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, urinalysis), vital signs or the ECG associated with VTE treatment.

8.2.1. 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.

8.2.2. 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 neutralizing antibodies.

8.2.3. 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.

8.2.4. 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. The sponsor proposes that proactive VTE2Q8 be administered from the sixth month of treatment onwards rather than reactive VTE PRN.

[information redacted]

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 (that is, Week 0-24 data for VTE2Q4 versus sham and post hoc justification analysis for ≥ 4 VTE injections sub-group). 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.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of Eylea, given the proposed usage, is favourable.

9. First round recommendation regarding authorisation

a. It is recommended that EYLEA be approved for the **treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRV0).** 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.

b. It is recommended that the approved dosage be one IVT injection (2 mg) every 4 weeks (VTE2Q4) rather than one IVT injection (2 mg) every two months (that is, VTE2Q8) following the first six months of treatment with VTE2Q4. The recommendation for a continuous VTE2Q4 treatment regimen has been inferred from the available safety data from COPERNICUS and GALILEO.

10. Clinical questions

10.1. Pharmacokinetics

No questions.

10.2. Pharmacodynamics

No questions.

10.3. Efficacy

c. 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?

d. 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.

10.4. Safety

e. 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.

f. In the sponsor's Summary of Clinical Safety (Table 22[11]; 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.

g. In the COPERNICUS CSR (Week 100), it is stated ("Prespecified ocular adverse events of special interest") that "From 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[12] 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[13] 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.

h. In the COPERNICUS CSR (Week 100), it is stated ("Prespecified 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[14] 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[15] 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.

10.4.1. Dosing regimen

i. The recommended Eylea dose in the US 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

[11] Not in this AusPAR
[12] Not in this AusPAR
[13] Not in this AusPAR
[14] Not in this AusPAR
[15] Not in this AusPAR

six months, followed by one injection (2 mg, 5 μL) every two months. Please comment on the reason for this difference.

j. 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 (that is, Week 0 to 24 data for VTE2Q4 versus sham, and posology justification analysis for the ≥ 4 VTE injections sub-group). 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.

11. Second round evaluation of clinical data submitted in response to questions

This is the second round clinical evaluation report (CER2) of the sponsor's Category 1 (PM-2012-03146-3-5) 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*".

In this second round CER, the sponsor's responses have been provided in full or have been summarised to include the key data and relevant information has been included in the report.

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 Category 1 submission to extend the indication to include macular oedema following CRVO.

11.1. Evaluation of the sponsor's response

11.1.1. Efficacy

11.1.1.1. Question a

11.1.1.1.1. 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).

11.1.1.1.2. 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.

11.1.1.2. Question b

11.1.1.2.1. 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.

[information redacted]

11.1.1.2.2. Evaluator's comment

The sponsor's response is acceptable. The data provided in the fourth paragraph of the sponsor's response refers to the pooled VTE2Q4+PRN group [information redacted]. 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).

[information redacted]

11.1.2. Safety

11.1.2.1. Question c

11.1.2.1.1. Sponsor's response

As stated in the 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.

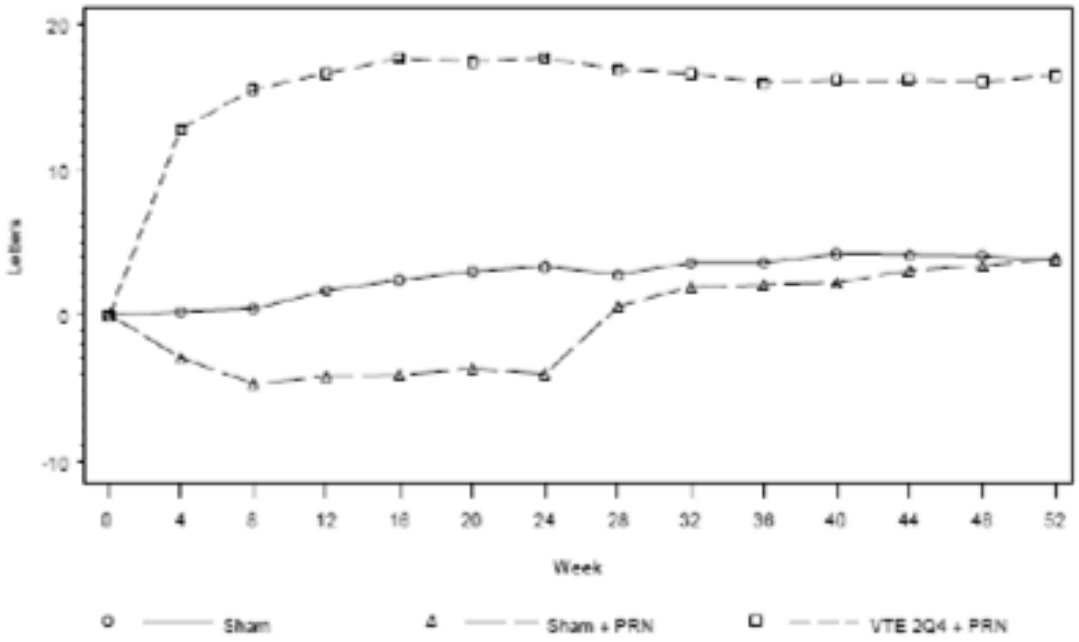
As noted by the evaluator, macular oedema and reduced visual acuity was reported as a TEAE in 44 (21.3%) patients and 27 (13%) patients, respectively, in Week 24 to 52 according to the integrated analysis submitted with the original dossier. In depth analysis of all these cases of treatment emergent adverse event (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 5 below.

Figure 5. Change in BCVA Letter Score from Baseline Through Week 52



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.

11.1.2.1.2. Evaluator's comment

The sponsor's response is satisfactory.

11.1.2.2. Question d

11.1.2.2.1. Sponsor's response

The apparent discrepancies were due to an error in Table 22 in the 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 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 the source data.

11.1.2.2.2. Evaluator's comment

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

11.2. Dosing regimen

11.2.1. Question e

11.2.1.1. 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.

11.2.1.2. Evaluator's comment

The sponsor's response is satisfactory.

11.2.2. Question f

11.2.2.1. 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 dossier, see Study 14130 Week 76 CSR and Study VGFT-OD-0819 Week 100 CSR.

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. [information redacted].

To further address the question raised by the evaluator, additional analysis has been 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 hereby proposes 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.

Practically, the treatment would be initiated on a monthly schedule (details on duration discussed below). If the disease appears to be inactive according to the physician's judgment, the time interval to the next visit is extended in small increments (typically 1 to 2 weeks). If at the next visit after the extended interval the disease is still quiescent, the patient receives treatment and the time to the next visit is even further pushed out. If there are some signs of re-activation of the disease, the time interval between the visits is reduced to the last interval without disease re-activation. With a treat-and-extend paradigm, the disease is treated proactively at most visits. At the same time, the treatment interval is adjusted to avoid over or under treatment and also ascertains that patient safety is well controlled.

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.

11.2.2.1.1. 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 6) as well as on the time course of mean changes in BCVA (Figure 7).

Figure 6: Percent patients who gained ≥ 15 letters

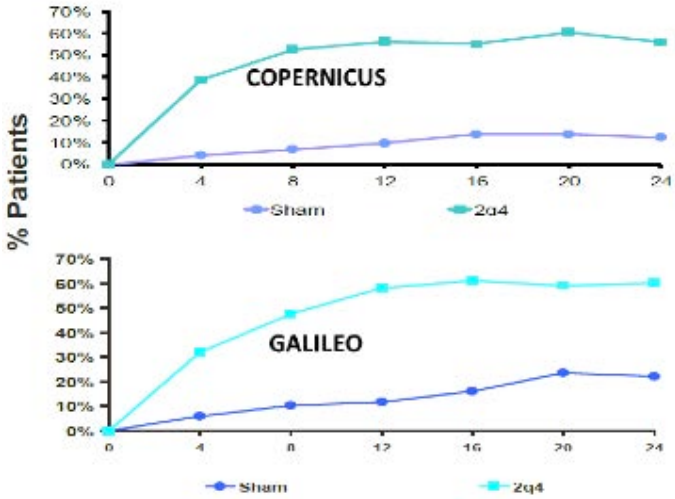
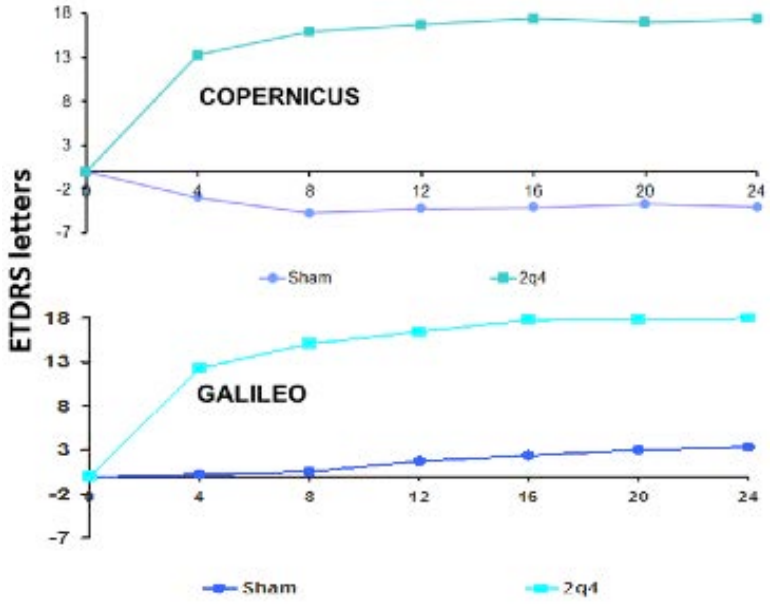


Figure 7. Mean change in visual acuity



[information redacted]

11.2.2.1.2. 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.

11.2.2.1.3. 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 (ie, 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 37 [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.

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 37 are relatively small, any conclusions must be drawn with caution.

11.2.2.1.4. Table 38 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).

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 were 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 38 are relatively small, again any conclusions must be drawn with caution.

Table 37: 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: **Number** of subjects **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** N (%)
Excellent (n = 107)			
Positive slope	52 (48.6%) 2 (1 - 4)	22 (20.6%) 3 (2 - 4)	4 (1.9%) 0 (0 - 0.5)
Negative slope	11 (10.3%) 1 (1 - 3)	18 (16.8%) 3 (3 - 4)	
Good (n = 31)			
Positive slope	12 (38.7%) 1.5 (1 – 3.5)	8 (25.8%) 2.5 (2 - 4)	0
Negative slope	6 (19.4%) 1.5 (1 - 2)	5 (16.1%) 3 (2 – 3)	
Modest (n = 31)			
Positive slope	14 (45.2%) 2 (2 – 3)	5 (16.1%) 3 (0 – 5)	1 (3.2%) 0 (0 – 0)
Negative slope	6 (19.4%) 3 (0 – 4)	5 (16.1%) 2 (1 – 3)	
Poor (n = 15)			
Positive slope	6 (40.0%) 3 (1 – 4)	2 (13.3%) 5 (3 – 7)	0
Negative slope	0	7 (46.7%) 3 (3 – 5)	
No stable gain (n = 19)			
Positive slope	4 (21.1%) (4.5 – 2.0)	4 (21.1%) 3 (2.5 – 3.5)	1 (5.3%) 2 (2 – 2)
Negative slope	4 (21.1%) 1.5 (0.5 – 2.0)	6 (31.6%) 2.5 (1 – 4)	
Missing (n = 4)			
Positive slope	0	0	2 (50.0%) 0 (0 – 0)
Negative slope	0	2 (50.0%) 3 (2 – 4)	
Total (n = 207)			
Positive slope	88 (42.5%) 2 (1 – 4)	41 (19.8%) 3 (2 – 4)	8 (3.9%) 0 (0 – 0.5)
Negative slope	27 (13.0%) 2 (1 – 3)	43 (20.8%) 3 (2 – 4)	

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

Table 38: 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).

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

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

[NB - Evaluator Comment: The superscript "b" for Table 38 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.]

11.2.2.1.5. 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.

11.2.2.1.6. Proposed changes to the recommended dosage regimen

Based on all of the above, the sponsor hereby proposes [information redacted] 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 is proposed in the present response package:

> *"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."*

[information redacted]

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 our 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 to Round 2 of CER.

11.2.2.2. Evaluator's comment

[information redacted]

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 8 and 9.

Figure 8: Copernicus – Study design.

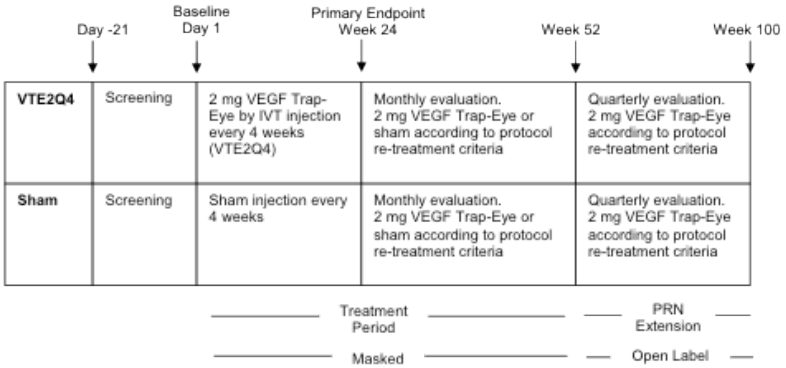
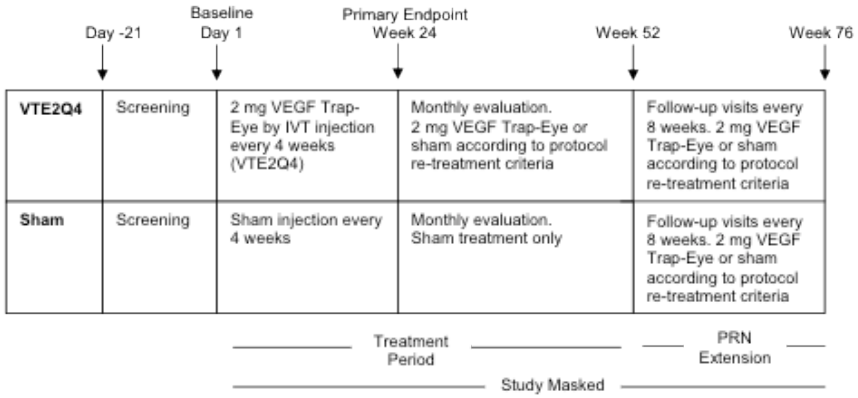


Figure 9: GALILEO – Study design



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. [information redacted]"*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's discussed its 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*". [information redacted].

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. [information redacted] 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 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.

12. 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 undertreat 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 is 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.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au