Table 20. Post-Randomization Ocular TEAEs Reported by >3 Subjects in Either Group, Study Eye (All Randomized Set)

Preferred Term[a] MedDRA, Version 13.0	Vial (N=50) n (%)	PFS (N=99) n (%)	Total (N=149) n (%)
No. of Subjects with Events, n (%)	38 (76.0)	58 (58.6)	96 (64.4)
Retinal haemorrhage	8 (16.0)	8 (8.1)	16 (10.7)
Cataract	7 (14.0)	9 (9.1)	16 (10.7)
VA reduced	8 (16.0)	7 (7.1)	15 (10.1)
Conjunctival haemorrhage	6 (12.0)	8 (8.1)	14 (9.4)
Vitreous floaters	2 (4.0)	7 (7.1)	9 (6.0)
Blepharitis	5 (10.0)	2 (2.0)	7 (4.7)
Macular degeneration	3 (6.0)	4 (4.0)	7 (4.7)
Foreign body sensation in eyes	0	6 (6.1)	6 (4.0)
Vitreous detachment	5 (10.0)	1 (1.0)	6 (4.0)
Eye pain	1 (2.0)	3 (3.0)	4 (2.7)
Eye pruritus	0	4 (4.0)	4 (2.7)
Injection site pain	0	4 (4.0)	4 (2.7)
IOP increased	0	4 (4.0)	4 (2.7)

Study VGFT-OD-0706/13336 (DAVINCI), ocular TEAEs in the study eye were reported in 26 (59.1%) subjects with aflibercept 0.5 mg q4w, 20 (45.5%) subjects with 2 mg q4w, 23 (54.8%) subjects with 2 mg q8w, 19 (42.2%) subjects with 2 mg PRN and 21 (47.7%) subjects with laser. The pattern of TEAEs in the study was similar for all five treatment groups. Ocular procedure related TEAEs were reported in 16 (36.4%) subjects with aflibercept 0.5 mg q4w, eleven (25.0%) subjects with 2 mg q4w, 17 (40.5%) subjects with 2 mg q8w, 19 (42.2%) subjects with 2 mg PRN and 14 (31.1%) subjects with laser. Ocular TEAEs in the fellow eye were reported in 14 (31.8%) subjects with aflibercept 0.5 mg q4w, seven (15.9%) subjects with 2 mg q4w, 13 (31.0%) subjects with 2 mg q8w, 13 (28.9%) subjects with 2 mg PRN and eight (18.2%) subjects with laser. Conjunctival haemorrhage, eye pain and ocular hyperaemia were more common in the treated eye than the fellow eye. Non-ocular TEAEs were reported in 14 (31.8%) subjects with aflibercept 0.5 mg q4w, 32 (72.7%) subjects with 2 mg q4w, 24 (54.5%) subjects with 2 mg q8w, 26 (61.9%) subjects with 2 mg PRN and 27 (60.0%) subjects with laser. The pattern of non-ocular TEAEs was similar for the five treatment groups. TEAEs of interest occurred to a greater extent in the aflibercept groups: 27 (15.4%) subjects overall compared with three (6.8%) subjects in the laser group (Table 21). Two subjects in the aflibercept 2 mg q4w group had an increase in IOP of ≥10 mmHg from baseline at Week 24.

Table 21. Treatment-Emergent Adverse Events of Interest (SAF).

Preferred Term[a]	Laser (N=44) n (%)	0.5 q4 (N=44) n (%)	2.0 q4 (N=44) n (%)	2.0 q8 (N=42) n (%)	2.0 PRN (N=45) n (%)	All VEGF Trap-Eye (N=175) n (%)
Total No. of Events, n	3	13	10	3	7	33
Total No. of Patients, n (%)	3 (6.8)	11 (25.0)	8 (18.2)	2 (4.8)	6 (13.3)	27 (15.4)
Hypertension	3 (6.8)	2 (4.5)	4 (9.1)	1 (2.4)	3 (6.7)	10 (5.7)
Blood pressure increased	0	2 (4.5)	2 (4.5)	1 (2.4)	1 (2.2)	6 (3.4)
Anterior chamber cell	0	3 (6.8)	0	0	0	3 (1.7)
Iritis	0	1 (2.3)	0	0	1 (2.2)	2 (1.1)
Endophthalmitis	0	0	1 (2.3)	0	1 (2.2)	2 (1.1)
Cerebrovascular accident	0	1 (2.3)	1 (2.3)	0	0	2 (1.1)
Hypertensive emergency	0	0	1 (2.3)	0	0	1 (0.6)
Anterior chamber flare	0	1 (2.3)	0	0	0	1 (0.6)
Uveitis	0	1 (2.3)	0	0	0	1 (0.6)
Vitritis	0	0	0	0	1 (2.2)	1 (0.6)
Myocardial infarction	0	1 (2.3)	0	0	0	1 (0.6)
Silent myocardial infarction	0	0	1 (2.3)	0	0	1 (0.6)
Epistaxis	0	1 (2.3)	0	0	0	1 (0.6)

[a] Events are presented in decreasing order of frequency in the All VEGF Trap-Eye column.

Serious adverse events and deaths

Study VGFT-OD-0502/14395 Part A, no serious adverse events (SAEs) occurred during the treatment phase but SAEs were reported for three subjects during the extended follow-up phase. One subject in the 1.0 mg cohort had atrial fibrillation, bradycardia, acute renal failure and pneumonia. One subject in the 2.0 mg cohort had cerebral infarction, angina pectoris, and esophageal dyskinesia and this patient subsequently withdrew from the study because of medical issues. One subject in the 4.0 mg cohort had prostate cancer. A further two subjects had SAEs during the open-label extension: breast cancer and retinal detachment.

Study VGFT-OD-0502/14395 Part C, there were no ocular SAEs. For the entire study, eight (28.6%) subjects reported systemic SAEs: squamous cell carcinoma of the skin in two patients; colon cancer, congestive cardiac failure in two patients, lobar pneumonia; fall/contusion/facial bones fracture; and hydronephrosis/urinary retention.

Study VGFT-OD-0603, a total of 19 SAEs were reported in eight subjects. None of the SAEs appeared to be related to treatment.

Study VGFT-OD-0603, one subject in the IVT-1 cohort died 47 days after the last dose of study drug due to cardiac arrest.

Study VGFT-OD-0512, two subjects reported SAEs: one with coronary artery disease and one with streptococcal cellulites/ acute renal failure/ anemia/ peripheral ischemia/ osteomyelitis.

Study VGFT-OD-0305, SAEs were reported in three subjects: one placebo, one given 0.3 mg/kg and one given 3.0 mg/kg. The event in the 3.0 mg/kg subject was malignant hypertension, which was considered to be a dose-limiting toxicity. A second subject with proteinuria was also considered to have a dose limiting toxicity. Two subjects experienced serious ocular adverse events: both retinal haemorrhage.

Study VGFT-OD-0306, one subject reported a SAEs: fall/ left hip fracture.

Study VGFT-OD-0508, SAEs were reported in eleven (34.4%) subjects in the 0.5 mg q4w group, five (15.6%) subjects in the 0.5 mg q12w group, ten (32.3%) subjects in the 2 mg

q4w group, seven (22.6%) subjects in the 2 mg q12w group and two (6.5%) subjects in the 4 mg q12w group. One subject in the 0.5 mg q4w group developed suspected culture-negative endophthalmitis that was reported as an SAE of uveitis after receiving the fifth injection of study treatment.

Study VGFT-OD-0508, there were two deaths: one in the 2 mg q4w group (pancreatic carcinoma) and one in the 4 mg q12w group (pulmonary hypertension).

Study VGFT-OD-0605/14393 (VIEW 1), SAEs were reported in 49 (16.1%) subjects in the aflibercept 2 mg q4w group, 58 (19.1%) subjects in the 0.5 mg q4w group, 58 (19.1%) subjects in the 2 mg q8w group and 71 (23.4%) subjects in the ranibizumab group. Ocular SAEs in the study eye were reported in seven (2.3%) subjects in the aflibercept 2 mg q4w group, six (2.0%) subjects in the 0.5 mg q4w group, three (1.0%) subjects in the 2 mg q8w group and ten (3.3%) subjects in the ranibizumab group. Ocular SAEs in the fellow eye were reported in no subjects in the aflibercept 2 mg q4w group, three (1.0%) subjects in the 0.5 mg q4w group, two (0.7%) subjects in the 2 mg q8w group and three (1.0%) subjects in the ranibizumab group. Non-ocular SAEs were reported in 49 (16.1%) subjects in the aflibercept 2 mg q4w group, 58 (19.1%) subjects in the 0.5 mg q4w group, 58 (19.1%) subjects in the 2 mg q8w group and 71 (23.4%) subjects in the ranibizumab group. The pattern of non-ocular SAEs was similar for the four study groups and as expected given the age range of the subjects.

Study VGFT-OD-0605/14393 (VIEW 1), death was reported in one (0.3%) subject in the aflibercept 2 mg q4w group, one (0.3%) subject in the 0.5 mg q4w group, seven (2.3%) subjects in the 2 mg q8w group and five (1.6%) subjects in the ranibizumab group.

Study 311523 (VIEW 2), treatment emergent SAEs were reported in 49 (15.9%) subjects in the aflibercept 2 mg q4w group, 41 (13.8%) subjects in the 0.5 mg q4w group, 48 (15.6%) subjects in the 2 mg q8w group and 35 (12.0%) subjects in the ranibizumab group. Ocular treatment emergent SAEs in the study eye occurred in six (1.9%) subjects in the aflibercept 2 mg q4w group, five (1.7%) subjects in the 0.5 mg q4w group, nine (2.9%) subjects in the 2 mg q8w group and nine (3.1%) subjects in the ranibizumab group. Ocular treatment emergent SAEs in the fellow eye occurred in nine (2.9%) subjects in the aflibercept 2 mg q4w group, two (0.7%) subjects in the 0.5 mg q4w group, three (1.0%) subjects in the 2 mg q8w group and three (1.0%) subjects in the ranibizumab group. Non-ocular treatment emergent SAEs occurred in 36 (11.7%) subjects in the aflibercept 2 mg q4w group, 37 (12.5%) subjects in the 0.5 mg q4w group, 38 (12.4%) subjects in the 2 mg q8w group and 26 (8.9%) subjects in the ranibizumab group (Table 22).

Table 22. Non-ocular treatment-emergent SAEs occurring in at least 2 subjects in any treatment group (safety analysis set)

System organ class MedDRA preferred term	Ranibizumab	VEGF Trap-Eye			
	0.5Q4 (N = 291) n (%)	2Q4 (N = 309) n (%)	0.5Q4 (N = 297) n (%)	2Q8 (N = 307) n (%)	Combined (N = 913) n (%)
Any non-ocular serious TEAE	26 (8.9)	36 (11.7)	37 (12.5)	38 (12.4)	111 (12.2)
Cardiac disorders	**5 (1.7)**	**8 (2.6)**	**7 (2.4)**	**11 (3.6)**	**26 (2.8)**
Myocardial infarction	2 (0.7)	0 (0.0)	3 (1.0)	3 (1.0)	6 (0.7)
Acute coronary syndrome	0 (0.0)	2 (0.6)	2 (0.7)	1 (0.3)	5 (0.5)
Atrial fibrillation	2 (0.7)	1 (0.3)	0 (0.0)	3 (1.0)	4 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (1.0)**	**3 (1.0)**	**9 (3.0)**	**5 (1.6)**	**17 (1.9)**
Breast cancer	1 (0.3)	0 (0.0)	3 (1.0)	1 (0.3)	4 (0.4)
Basal cell carcinoma	1 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.2)
Gastrointestinal disorders	**0 (0.0)**	**4 (1.3)**	**6 (2.0)**	**6 (2.0)**	**16 (1.8)**
Injury, poisoning and procedural complications	**2 (0.7)**	**1 (0.3)**	**7 (2.4)**	**6 (2.0)**	**14 (1.5)**
Upper limb fracture	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.2)
Fall	2 (0.7)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Nervous system disorders	**2 (0.7)**	**8 (2.6)**	**2 (0.7)**	**3 (1.0)**	**13 (1.4)**
Cerebrovascular accident	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.7)	3 (0.3)
Transient ischaemic attack	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.2)
Infections and infestations	**6 (2.1)**	**4 (1.3)**	**0 (0.0)**	**8 (2.6)**	**12 (1.3)**
Pneumonia	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.7)	4 (0.4)
Respiratory, thoracic and mediastinal disorders	**1 (0.3)**	**4 (1.3)**	**1 (0.3)**	**2 (0.7)**	**7 (0.8)**
General disorders and administration site conditions	**3 (1.0)**	**4 (1.3)**	**1 (0.3)**	**1 (0.3)**	**6 (0.7)**
Vascular disorders	**2 (0.7)**	**2 (0.6)**	**2 (0.7)**	**2 (0.7)**	**6 (0.7)**
Musculoskeletal and connective tissue disorders	**2 (0.7)**	**3 (1.0)**	**0 (0.0)**	**2 (0.7)**	**5 (0.5)**
Skin and subcutaneous tissue disorders	**2 (0.7)**	**1 (0.3)**	**2 (0.7)**	**1 (0.3)**	**4 (0.4)**
Hepatobiliary disorders	**0 (0.0)**	**2 (0.6)**	**1 (0.3)**	**0 (0.0)**	**3 (0.3)**
Renal and urinary disorders	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**2 (0.7)**	**3 (0.3)**
Investigations	**0 (0.0)**	**2 (0.6)**	**0 (0.0)**	**0 (0.0)**	**2 (0.2)**
Surgical and medical procedures	**2 (0.7)**	**0 (0.0)**	**1 (0.3)**	**1 (0.3)**	**2 (0.2)**
Metabolism and nutrition disorders	**2 (0.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**

Note: System organ classes (SOCs) as well as preferred terms within each SOC are sorted in descending order by frequency in the VEGF Trap-Eye combined group.

Study 311523 (VIEW 2), there were nine deaths in total: three (1.0%) subjects in the aflibercept 2 mg q4w group, two (0.7%) subjects in the 0.5 mg q4w group, two (0.7%) subjects in the 2 mg q8w group and two (0.7%) subjects in the ranibizumab group.

StudyVGFT-OD-0702/14262, SAEs were reported in 64 (40.8%) subjects. Ocular SAEs were reported in eight (5.1%) subjects. Non-ocular SAEs were reported in 59 (37.6%) subjects. Procedure related SAEs were reported in two (1.3%) subjects.

StudyVGFT-OD-0702/14262, eight (5.1%) subjects died but none of the deaths appeared to be related to study treatment.

Study VGFT-OD-0706/13336 (DAVINCI), SAEs were reported in seven (15.9%) subjects in the aflibercept 0.5 mg q4w group, nine (20.9%) subjects in the 2 mg q4w group, eight (19.0%) subjects in the 2 mg q8w group, three (6.7%) subjects in the 2 mg PRN group and six (13.6%) subjects in the laser group. There were more infections reported as SAEs in the aflibercept groups: nine (5.1%) subjects compared with none in the laser group. Ocular SAEs in the study eye were reported in one (2.3%) subject with aflibercept 0.5 mg

q4w, one (2.3%) subject with 2 mg q4w, one (2.4%) subject with 2 mg q8w, one (2.2%) subject with 2 mg PRN and three (6.8%) subjects with laser. Ocular SAEs in the fellow eye were reported in one (2.4%) subject with 2 mg q8w. Non-ocular SAEs were reported in six (13.6%) subjects with aflibercept 0.5 mg q4w, eight (18.2%) subjects with 2 mg q4w, six (14.3%) subjects with 2 mg q8w, two (4.4%) subjects with 2 mg PRN and three (6.8%) subjects with laser.

Study VGFT-OD-0706/13336 (DAVINCI), death was reported in one (2.3%) patient with aflibercept 0.5 mg q4w (multi-organ failure), one (2.3%) patient with 2 mg q4w (sudden unexplained), and one (2.4%) patient with 2 mg q8w (convulsions).

There were no SAEs reported in *Study VGFT-OD-0502/14395 Part B, Study VGFT-OD-0307, Study PDY6655 or Study PDY6656.*

There were no deaths reported in *Study VGFT-OD-0502/14395 Part A, Part B and Part C*; or in *Study VGFT-OD-0512*, *Study VGFT-OD-0305*, *Study VGFT-OD-0306*, *Study VGFT-OD-0307*, *Study PDY6655 and Study PDY6656*.

Laboratory findings

Study VGFT-OD-0502/14395 Part A, there was one clinically significant abnormality in a laboratory test: elevated creatinine kinase to 923 U/L.

Studies VGFT-OD-0502/14395 Part B and Part C, there were no clinically significant laboratory abnormalities.

Study VGFT-OD-0603, one subject was reported with a urinary tract infection (UTI) and one with hypokalaemia. Both abnormalities resolved.

Study VGFT-OD-0512, laboratory test abnormalities were consistent with the subjects' history of diabetes.

Study VGFT-OD-0305, proteinuria was reported in 5 patients: 2 in the 1.0 mg/kg group and 3 in the 3.0 mg/kg group. Haematuria was reported in one subject in the VEGF Trap 1.0 mg/kg group

Study VGFT-OD-0306, proteinuria was reported in six (85.7%) subjects.

Study VGFT-OD-0307 , one subject had proteinuria related to treatment

Study PDY6655, one subject had elevated alanine aminotransferase (ALT) (155.8 IU/L) and one had elevated aspartate aminotransferase (AST) (98 IU/L).

Study PDY6656, one subject in the 4 mg/kg group had an elevation of AST to 101 IU/L on Day 43 that had normalised by the end of study. One subject in the placebo group and one subject in the 2 mg/kg group had decreases in neutrophil count that had normalised by the end of study.

Study VGFT-OD-0508, there were few clinically significant laboratory tests abnormalities and these did not appear to be dose or frequency related. The majority of plasma samples assayed for free aflibercept concentrations were below the lower limit of quantification (LLOQ),

Study VGFT-OD-0605/14393 (VIEW 1), the pattern of abnormal test results was similar for all three treatment groups and compatible with the age range of the study subjects. Shift in urine protein creatinine ratio from normal at baseline to high at Week 52 was reported for 30 (16.9%) subjects in the aflibercept 2 mg q4w group, 34 (21.1%) subjects in the 0.5 mg q4w group, 26 (15.3%) subjects in the 2 mg q8w group and 35 (19.7%) subjects in the ranibizumab group.

Study 311523 (VIEW 2), the pattern of significant abnormalities in laboratory tests was similar for all four treatment groups.

StudyVGFT-OD-0702/14262, there were no clinically significant laboratory test abnormalities.

Study VGFT-OD-0706/13336 (DAVINCI), abnormalities in laboratory tests were uncommon and did not indicate any association with study treatment. Six (3.4%) subjects in the aflibercept groups developed proteinuria compared with none in the laser group.

Safety in special populations

Older persons were well represented in the study population. There were no data provided from the paediatric population or during pregnancy.

Immunological events

Study VGFT-OD-0502/14395 Part A, one subject developed anti-aflibercept antibodies (concentration <1.2 mg/L).

Study VGFT-OD-0605/14393 (VIEW 1), a positive anti-drug antibody assay was reported in 13 (4.3%) subjects in the aflibercept 2 mg q4w group, eleven (3.6%) subjects in the 0.5 mg q4w group, six subjects in the 2 mg q8w group and 15 (4.9%) subjects in the ranibizumab group. One subject in the aflibercept 2 mg q4w group exhibited neutralising activity. The presence of anti-drug antibody did not appear to influence efficacy (Table 23).

Table 23. Supportive Analysis of the Proportion of Subjects with Maintained Vision at Week 52 by Anti-VEGF Trap Antibodies Status, LOCF (Per Protocol Set)

Sub Group	Treatment Group	Subjects who Maintained Vision at week 52 n (%)	Difference [1] % (95.1 % C.I.)
POSITIVE	VTE 2Q4 (N = 13)	11 (84.6%)	8.7 (-14.7, 32.1)
	R 0.5Q4 (N = 15)	14 (93.3%)	
	VTE 0.5Q4 (N = 11)	10 (90.9%)	2.4 (-18.8, 23.7)
	R 0.5Q4 (N = 15)	14 (93.3%)	
	VTE 2Q8 (N = 6)	6 (100%)	-6.7 (-19.3, 6)
	R 0.5Q4 (N = 15)	14 (93.3%)	
NEGATIVE	VTE 2Q4 (N = 272)	260 (95.6%)	-1.1 (-4.9, 2.6)
	R 0.5Q4 (N = 253)	239 (94.5%)	
	VTE 0.5Q4 (N = 259)	249 (96.1%)	-1.7 (-5.4, 2)
	R 0.5Q4 (N = 253)	239 (94.5%)	
	VTE 2Q8 (N = 259)	246 (95.0%)	-0.5 (-4.4, 3.4)
	R 0.5Q4 (N = 253)	239 (94.5%)	

Study 311523 (VIEW 2), systemic reactions related to immunogenicity were reported in two (0.6%) subjects in the aflibercept 2 mg q4w group, four (1.3%) subjects in the 0.5 mg q4w group, five (1.6%) subjects in the 2 mg q8w group and seven (2.4%) subjects in the ranibizumab group. There were no anaphylactic reactions reported in the aflibercept groups whereas one anaphylactic reaction was reported in the in the ranibizumab gorup. Anti-drug antibodies were detected in 16 (5.4%) subjects in the aflibercept 2 mg q4w group, 15 (4.9%) subjects in the 0.5 mg q4w gorup, three (1.0%) subjects in the 2 mg q8w group and eight (2.7%) subjects in the ranibizumab group. No subject was detected with neutralising anti-drug antibodies. Antibody status did not appear to influence efficacy (Table 24).

Table 24. Proportion of subjects with maintained vision at Week 52 by AB positive/negative, LOCF (Full analysis set)

AB development flag_n	Treatment group	Subjects with maintained vision at week 52(%)	Difference [1](95 % c.i.)
N	VTE2Q4(N=285)	270(94.74)	-0.09(-3.79,3.60)
	R0.5Q4(N=280)	265(94.64)	
	VTE0.5Q4(N=277)	264(95.31)	-0.66(-4.29,2.96)
	R0.5Q4(N=280)	265(94.64)	
	VTE2Q8(N=302)	288(95.36)	-0.72(-4.27,2.83)
	R0.5Q4(N=280)	265(94.64)	
Y	VTE2Q4(N=15)	13(86.67)	13.33(-3.87,30.54)
	R0.5Q4(N=8)	8(100.00)	
	VTE0.5Q4(N=15)	14(93.33)	6.67(-5.96,19.29)
	R0.5Q4(N=8)	8(100.00)	
	VTE2Q8(N=3)	3(100.00)	
	R0.5Q4(N=8)	8(100.00)	

Anti aflibercept antibodies were not detected in *Study VGFT-OD-0502/14395 Part B, Study VGFT-OD-0512, Study VGFT-OD-0305, Study VGFT-OD-0306, Study VGFT-OD-0307, Study PDY6655, Study PDY6656, Study VGFT-OD-0508, StudyVGFT-OD-0702/14262 or Study VGFT-OD-0706/13336.*

Safety related to drug-drug interactions and other interactions

No data with regard to drug-drug interactions were included in the submission.

Discontinuation due to adverse events

Study VGFT-OD-0502/14395 Part A, (as discussed above) one subject in the 2.0 mg cohort had cerebral infarction, angina pectoris and esophageal dyskinesia and subsequently withdrew from the study because of medical issues.

Study VGFT-OD-0502/14395 Part C, one subject withdrew because of a low platelet count that had been present from baseline.

Study VGFT-OD-0305, three subjects discontinued due to AEs (DAE): two in the 3.0 mg/kg group (hypertension and malignant hypertension) and one in the 1 mg/kg group (headache/ hypertension/ proteinuria).

Study VGFT-OD-0306, one subject withdrew because of a TEAE: hypertension.

Study VGFT-OD-0307, two subjects in the placebo group withdrew due to TEAEs.

Study PDY6655, two subjects discontinued due to AEs following subcutaneous administration: delayed allergic dermatitis at the injection site; and multiple trauma caused by car accident.

Study VGFT-OD-0508, DAE occurred for seven subjects overall: one (3.1%) in the 0.5 mg q4w group, three (9.4%) in the 0.5 mg q12w group, none in the 2 mg q4w group, 2 (6.5%) in the 2 mg q12w group and one (3.2%) in the 4 mg q12w group. Two of the DAEs were considered to be treatment related: retinal haemorrhage and retinal oedema.

Study VGFT-OD-0605/14393 (VIEW 1), AEs leading to the discontinuation of study treatment was reported in three (1.0%) subjects in the aflibercept 2 mg q4w group, five (1.6%) subjects in the 0.5 mg q4w group, three (1.0%) subjects in the 2 mg q8w group and five (1.6%) subjects in the ranibizumab group.

Study 311523 (VIEW 2) TEAE leading to discontinuation of study treatment was reported in twelve (3.9%) subjects in the aflibercept 2 mg q4w group, 14 (4.7%) subjects in the 0.5 mg q4w group, ten (3.3%) subjects in the 2 mg q8w group and four (1.4%) subjects in the ranibizumab group.

StudyVGFT-OD-0702/14262, three (2%) subjects permanently discontinued study treatment: macular degeneration; reduced visual acuity; and metastatic non-small cell lung cancer.

Study VGFT-OD-0706/13336 (DAVINCI), DAE was reported in one (2.3%) subject with aflibercept 0.5 mg q4w (uveitis).

There were no withdrawals due to TEAEs in *Study VGFT-OD-0502/14395 Part B, Study VGFT-OD-0603, Study VGFT-OD-0512 or Study PDY6656*.

Additional safety data

Study VGFT-OD-0910/14832 is an open label, long term safety and tolerability study follow-on to Study VGFT-OD-0605. The study includes subjects with neovascular AMD that have completed Study VGFT-OD-0605. The study is ongoing and a report was not provided with the current submission. Limited data were provided in the sponsor's Summary of Clinical Safety. The study treatment is aflibercept 2 mg PRN, but at least every 12 weeks, by intravitreal injection with an injection volume of 50 µL. The study is of 18 months duration. A total of 178 subjects had been recruited. Three SAEs were reported in the sponsor's Summary of Clinical Safety: device dislocation; renal cancer and urinary tract infection.

Study VGFT-OD-0819/14232 (COPERNICUS) is a randomised double masked sham controlled study the efficacy and safety of aflibercept in central retinal venous occlusion (CRVO). The study is ongoing. The study includes subjects at least 18 years of age with centre involved macular edema secondary to CRVO with mean central retinal thickness ≥250 µm on OCT. The study treatments were: aflibercept 2 mg q4w by intravitreal injection in comparison with sham injections q4w. Efficacy data were not reported. SAEs reported to date were included in the sponsor's Summary of Clinical Safety. A total of 189 subjects had been recruited. There were 58 SAEs reported in 29 (15.4%) subjects. The most commonly reported SAEs were: vitreous haemorrhage in four (2.1%) subjects, glaucoma in two (1.1%) subjects, iris neovascularisation in two (1.1%) subjects, pneumonia in two (1.1%) subjects and retinal haemorrhage in two (1.1%) subjects.

Study 14130 (GALILEO) is a randomised double masked sham controlled study the efficacy and safety of aflibercept in CRVO. The study is ongoing. The study includes adults ≥ 18 years, with centre-involved macular edema secondary to CRVO for no longer than 9 months with mean central subfield thickness ≥ 250 µm on optical coherence tomography (OCT) and with ETDRS BCVA of 20/40 to 20/320 (73 to 24 letters) in the study eye. The study treatments were: aflibercept 2 mg q4w by intravitreal injection which was compared with sham injections q4w. Efficacy data were not reported. SAEs reported to date were included in the sponsor's Summary of Clinical Safety. A total of 177 subjects had been recruited. A total of 17 SAEs were reported in 13 (7.6%) subjects. No SAE was reported in more than one subject.

Post marketing experience

No postmarketing data were included with the current submission.

Evaluator's overall conclusions on clinical safety

Intravitreal aflibercept is associated with an increased rate of conjunctival haemorrhage, eye pain and reduction in visual acuity. These adverse events appear primarily to be due to the procedure of intravitreal injection rather than the local effects of aflibercept. There was an increase in IOP of around 3.2 mmHg immediately post treatment that did not increase with subsequent treatments. Ocular adverse events did not appear to be influenced by dose or dosing regimen. However, ocular AEs were more common with the

vial presentation than with the pre-filled syringe. A similar rate of ocular AEs was observed with ranibizumab.

Intravenous (high dose) aflibercept is associated with headache, hypertension, proteinuria and dysphonia. Hypertension was a dose limiting adverse event at a dose level of 3mg/kg.

The rates of SAE and death did not indicate any safety issues with aflibercept. The conditions leading to non-ocular SAE and death were as expected for the age group and general health of the population of subjects included in the studies. Ocular SAEs appeared to be related to the procedure of intravitreal injection and not to aflibercept.

The rates of clinical laboratory test abnormalities with intravitreal aflibercept were low and were consistent with the age and general health of the study population. Proteinuria appears to be associated with intravenous high dose aflibercept.

Less than 5% of the treatment population developed anti-aflibercept antibodies. The development of anti-aflibercept antibodies was not associated with loss of efficacy, immunological AEs or increased risk of AE.

There was a low rate of withdrawal from the clinical studies due to AE. This indicates that intravitreal aflibercept is well tolerated.

List of questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Efficacy

It is not clear from the clinical studies how the sponsor determined the final dosing recommendations in the product information document. The proposed dosing regimen (2 mg intravitreal injection each month for the first three injections followed by administration every second month) would provide the sponsor with a marketing advantage, that is, a perception that less frequent dosing is required. Hence, it is important that the dosing regimen is supported by data. Can the sponsor provide a justification for the dosing regimen proposed in the Product Information document?

The sponsor provided a response to this question (see *Response to the Clinical Evaluation Report*).

Clinical summary and conclusions

Clinical aspects

Eylea (aflibercept) is intended for intravitreal administration and systemic exposure is important from a safety perspective but not from an efficacy perspective. The systemic exposure following intravitreal injection was minimal in comparison with studies of intravenous aflibercept. This would be expected given the differences in total dose: up to 4 mg intravitreal compared with up to 4 mg/kg intravenous.

Following intravitreal injection of 2 mg aflibercept the exposure to free aflibercept, expressed as AUC_{last}, was median (range) 0.0221 (0 to 0.474) mg•day/L, and exposure to aflibercept:VEGF complex expressed as median AUC_{last}, was (range) 4.67 (2.12 to 6.71) mg•day/L (Study VGFT-OD-0702.PK). Following 4 mg intravitreal injection, for aflibercept: VEGF complex T_{max} was 12 weeks and the mean C_{max} was (SE) 0.236 (0.0302) mg/mL (Study VGFT-OD-0603). Following 4 mg intravitreal injection, the mean

concentrations of aflibercept were 0.0502 and 0.0272 mg/L on Days 3 and 8, respectively (Study VGFT-OD-0512).

Following intravenous administration, C_{max} for free aflibercept was 50 mg/L for a 3.0 mg/kg dose, around 16 mg/L for a 1.0 mg dose and 5 mg/L for a 0.3 mg/kg dose. The C_{max} for total aflinercept was 50 mg/L for the 3.0 mg/kg dose, around 15 mg/L for the 1.0 mg dose and 5 mg/L for the 0.3 mg/kg dose (Study VGFT-OD-0305).

Following 2.0 mg/kg aflibercept by intravenous or subcutaneous administration, the mean (CV%) AUC and C_{max} for free aflibercept were 177 (33) µg.day/mL and 44.4 (36) µg/mL, respectively, for intravenous whereas the AUC and C_{max} were 84.9 (30) µg.day/mL and 7.76 (39) µg/mL for subcutaneous administration. For bound aflibercept, the mean (CV%) AUC and C_{max} were 57.7 (19) µg.day/mL and 1.84 (22) µg/mL, respectively, for intravenous administration and 47.3 (27) µg.day/mL and 1.60 (27) µg/mL, respectively, for subcutaneous administration (Study PDY6655).

Following intravenous administration, the mean (CV%) C_{max} for free aflibercept was 18.2 (18) µg/mL for a 1 mg/kg dose, 39.7 (27) µg/mL for a 2 mg/kg dose and 78.6 (15) µg/mL for a 4 mg/kg dose. The mean (CV%) AUC was 64.8 (20) µg.day/mL for a 1 mg/kg dose, 180 (20) for a 2 mg/kg dose and 419 (21) for a 4 mg/kg dose (Study PDY6656). Bound aflibercept concentrations were not dose proportional but C_{max} and AUC for total aflibercept were dose proportional.

Aflibercept at high doses administered intravenously significantly increases blood pressure. However, the level of systemic exposure from intravitreal administration would not be sufficient to cause similar effects on blood pressure.

Intravenous or subcutaneous 2 mg/kg aflibercept increased SBP by a mean of up to 6.5 mmHg and DBP of up to 7.22 mmHg with a maximal effect at Day 16 post administration (Study PDY6655). SBP was increased by 10.27 (5.77 to 14.78) mmHg and DBP by 10.67 (7.68 to 13.66) mmHg by 4 mg/kg aflibercept administered intravenously (Study PDY6656). The increase in blood pressure persisted for up to 44 days at the 4 mg/kg dose level. Plasma renin activity and aldosterone concentrations were decreased.

Benefit risk assessment

Benefits

The primary efficacy measures used in the drug development program were clinically important and had been adequately validated. The efficacy outcome measures were refined during Phase I development. BCVA became the tool used to determine the primary efficacy outcome measures in the pivotal studies. The secondary efficacy measures (CRT and macular volume) assessed pathology and disease severity. Fluorescein angiography was not useful to demonstrate differences between treatments.

In the initial dose finding studies, the greatest effect was in the 2 mg to 4 mg dose grouping (Study VGFT-OD-0502/14395 Part A). Effect increased with increasing dose up to 4 mg. Peak effect appeared to be at Day 29 (Study VGFT-OD-0502/14395 Part C). Different formulations, volumes and concentrations of aflibercept were evaluated in Study VGFT-OD-0603/14396 (CLEAR-IT 1b), which enabled a 50 µL volume to be used in further studies.

There were some Phase I data of aflibercept administered intravenously. Study VGFT-OD-0305 indicated that a dose of 3 mg/kg aflibercept by intravenous injection was effective but that a dose of 1 mg/kg was not. Study VGFT-OD-0306 indicated that intravenous treatment with aflibercept would not be as effective long-term as intravitreal.

The Phase II study (Study VGFT-OD-0508/14394 [CLEAR-IT AMD-2]) did not clearly indicate the most appropriate dosing regimen. In the Phase II study the greatest reduction

in CRT at Week 12 was with a 2 mg q4w dosing regimen but at all other time points over 52 weeks the greatest reduction in CRT was with 4 mg q12w. The greatest improvement in BCVA through to Week 52 was with 2 mg q4w. However, the greatest improvement in vision related quality of life was with 4 mg q12w.

In the pivotal efficacy studies (Study VGFT-OD-0605/14393 [VIEW 1] and Study 311523 [VIEW 2]) the non-inferiority margin of 10% was appropriate as this would represent a clinically significant difference in treatment effect. The choice of comparator was appropriate. Ranibizumab is currently approved in Australia for the treatment of neovascular (wet) age-related macular degeneration and the dosing regimen used in the studies was consistent with the manufacturer's recommendations. The population studied was appropriate and representative of the patient population likely to require treatment. However, it is not clear whether blinding of the sham injections was maintained and the selection/allocation of study and fellow eyes was not randomised.

In the pivotal efficacy studies non-inferiority was demonstrated for all three aflibercept dosing regimens. In Study VGFT-OD-0605/14393 (VIEW 1), for the per-protocol group, the difference (95% CI) in proportion of subjects that maintained vision at Week 52 (ranibizumab – aflibercept) was –0.7 (–4.4 to 3.1) for 2 mg q4w, –1.5 (–5.1 to 2.1) for 0.5 mg q4w and –0.7 (–4.5 to 3.1) for 2 mg q8w. In Study 311523 (VIEW 2), for the per-protocol group, the difference (95% CI) in proportion of subjects that maintained vision at Week 52 (ranibizumab – aflibercept) was –1.2 (–4.86 to 2.46) for 2 mg q4w, –1.84 (-5.40 to 1.71) for 0.5 mg q4w and –1.13 (–4.81 to 2.55) for 2 mg q8w. The secondary efficacy outcome measures in both studies were supportive of the primary analysis.

In some of the additional efficacy outcome measures there were some differences between treatments in favour of the comparator:

Study VGFT-OD-0605/14393 (VIEW 1), the proportion of subjects showing complete resolution of FA leakage at Week 52 was significantly lower in the aflibercept 2 mg q8w group than in the ranibizumab group: 159 (52.8%) subjects compared with 193 (63.5%); difference (95% CI) -10.7 (-18.5 to -2.8) %, p=0.0084

Study 311523 (VIEW 2), for the change from baseline in BCVA at Week 12 there was a significant improvement in the ranibizumab group compared to the aflibercept 2 mg q4w group: LS mean difference (95% CI) -1.61 (-3.19 to -0.04) p=0.045.

Study 311523 (VIEW 2), the proportion of subjects with VA of 20/200 or worse at Week 52 was greater in the aflibercept 2 mg q4w group than in the ranibizumab group: difference (95% CI) 6.05 (1.25 to 10.86) p=0.014.

Study 311523 (VIEW 2), for the change from baseline in scores for NEI VFQ-25 distance activities ranibizumab was superior to aflibercept 2 mg q4w and 2 mg q8w; and for vision dependency ranibizumab was superior to aflibercept 2 mg q4w at Week 52.
However, there were also some additional efficacy outcome measures that were in favour of aflibercept:

Study 311523 (VIEW 2), the proportion of subjects showing complete resolution of FA leakage at Week 52 was significantly greater in the aflibercept 2 mg q4w group than in the ranibizumab group: 210 (67.96%) subjects compared with 162 (55.67%); difference (95% CI) 13.24 (5.60 to 20.89) %, p=0.0009.

Study 311523 (VIEW 2), there was a decrease in CRT in the aflibercept 2 mg q4w group compared to the ranibizumab group: LS mean difference (95% CI) -10.60 (-21.1 to -0.09) p=0.047.

The long term follow-on study, *StudyVGFT-OD-0702/14262*, did not contribute useful efficacy data because it was not possible to determine whether the rate of decline in visual function was modified by aflibercept. There were also some data for subjects with DME, a different indication to that sought in the present application (*Study VGFT-OD-0512/14805*

[CLEAR-IT DME 1] and Study VGFT-OD-0706/13336 (DAVINCI)). There were insufficient data to conclude efficacy. *Study VGFT-OD-0706/13336 (DAVINCI)* was supportive of efficacy but was conducted for a different indication than that applied for in the present application.

Risks

Intravitreal aflibercept is associated with an increased rate of conjunctival haemorrhage, eye pain and reduction in visual acuity. These adverse events appear primarily to be due to the procedure of intravitreal injection rather than the local effects of aflibercept. There was an increase in IOP of around 3.2 mmHg immediately post treatment that did not increase with subsequent treatments. Ocular adverse events did not appear to be influenced by dose or dosing regimen. However, ocular AEs were more common with the vial presentation than with the pre-filled syringe. A similar rate of ocular AEs was observed with ranibizumab.

Intravenous (high dose) aflibercept is associated with headache, hypertension, proteinuria and dysphonia. Hypertension was a dose limiting adverse event at a dose level of 3mg/kg.

The rates of SAE and death did not indicate any safety issues with aflibercept. The conditions leading to non-ocular SAE and death were as expected for the age group and general health of the population of subjects included in the studies. Ocular SAEs appeared to be related to the procedure of intravitreal injection and not to aflibercept.

The rates of clinical laboratory test abnormalities with intravitreal aflibercept were low and were consistent with the age and general health of the study population. Proteinuria appears to be associated with intravenous high dose aflibercept.

Less than 5% of the treatment population developed anti-aflibercept antibodies. The development of anti-aflibercept antibodies was not associated with loss of efficacy, immunological AEs or increased risk of AE.

There was a low rate of withdrawal from the clinical studies due to AE. This indicates that intravitreal aflibercept is well tolerated.

Balance

The risk-benefit balance is in favour of intravitreal aflibercept for the treatment of neovascular (wet) age-related macular degeneration (wet AMD).

Conclusions

It was recommended that the application for the following indication should be approved:

Eylea (aflibercept) is indicated for the treatment of neovascular (wet) age-related macular degeneration (wet AMD)

Recommended Conditions for Registration

There are a number of ongoing studies of intravitreal aflibercept being conducted by the sponsor. Registration should be conditional on the provision of timely updates of the safety and efficacy data from these studies and upon the performance of routine pharmacovigilance activities for Eylea (aflibercept).

V. Pharmacovigilance findings

Risk management plan

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

Safety specification

The summary Ongoing Safety Concerns as specified by the sponsor is as follows:

- **Important identified drug-related** risk: None
- **Important identified injection-related risks:** Endophthalmitis due to intravitreal injection
- **Important potential drug-related risks:**
  - Arterial thromboembolic events (ATEs)
  - Embryo-fetotoxicity
- **Important potential injection-related risk:** None
- **Important missing information:** Not identified

OPR reviewer comment

While 149 subjects completed study VGFT-OD-0702/14262 (long-term extension of the Phase I and II trials, treatment duration 38 months), the safety of IVT aflibercept in the long-term has not been established in a larger population. At this stage, safety has not been studied beyond 52 weeks in Phase III trials. It is therefore recommended that long-term safety be included as Important missing information in the Ongoing Safety Concerns. However, the sponsor has stated in a TGA response dated 24 October 2011 that

"it would not be appropriate to add 'absence of long-term safety experience' as missing information in the Australian Risk Management Plan as we believe the one year safety data submitted in support of product registration provides sufficient information with respect to establishing the safety profile of Eylea. This dataset.....indicate comparable safety profile between Eylea and the current standard of care, Lucentis, in the treatment of wet AMD. "

The sponsor has further elaborated that the following ongoing studies will provide data to support the long-term safety of Eylea:

a) two year repeated injections studies from pivotal Phase III randomised, double-masked, active controlled Study VGT-OD-0605 (VIEW 1) and Study 311523/91689 (VIEW 2) with data expected in first quarter of 2012,

b) a 18-month extension phase study for 323 VIEW 1 subjects, Study VGT-OD-0910 and

c) a three-year randomised and single-masked Study VGT-OD-0702/145262 with 157 subjects and data expected in first quarter of 2012.

Although it is agreed that the ongoing studies should inform of the long-term safety of Eylea beyond one year, the rationale provided by the sponsor on the comparable safety profile between Eylea and Lucentis in the treatment of wet AMD was not adequate to preclude the inclusion of Eylea's long-term safety as an Important missing information in the Ongoing Safety Concerns, considering the current lack of supporting data for Eylea's safety beyond one year. Furthermore, it is noted that the Australian Public Assessment Report for Ranibizumab (Lucentis) has identified long-term safety beyond two years as

Important missing information in Ongoing Safety Concerns for Lucentis[13]. With regard to the nonclinical and clinical evaluation reports, the above summary of the Ongoing Safety Concerns is therefore considered acceptable with the inclusion of long-term safety as Important missing information.

Pharmacovigilance plan

Proposed pharmacovigilance activities

It is proposed that routine pharmacovigilance[14] (PhV) activities will be supported by targeted follow-up of any post-market or study reports suspicious of intraocular infection by using a questionnaire. There will be a cumulative presentation and evaluation of reports of each of the Ongoing Safety Concerns in the Periodic Safety Update Reports (PSURs). Further data on intraocular infection and ATEs will be collected from the ongoing Phase III clinical trial program (for AMG and central retinal vein occlusion - CRVO). The protocols of these studies have not been reviewed as they are ongoing.

OPR reviewer's comments in regard to the pharmacovigilance plan and the appropriateness of milestones

The use of targeted follow-up seems appropriate to monitor the endophthalmitis safety concern, in particular to ensure a standard approach to collecting information. The details collected as part of the follow-up questionnaire have been provided in response to a TGA request for information dated 24 October 2011. The information requested in this questionnaire includes the details of the event, patient's history and injection procedure, which is appropriate to monitor the risk of endophthalmitis associated with an IVT procedure.

The incidence of stroke and myocardial infarction (MI) in AMD patients has been estimated using the United States Medicare database. The incidence of MI in patients with neovascular AMD has been estimated to be 2.2% annually and 4.09% over 2 years. The incidence of stroke in patients with neovascular AMD has been estimated to be 3.8% annually and 8.15% over 2 years.[15] Therefore, considering the sample sizes of the ongoing clinical trials, in particular VIEW 1, VIEW 2 and VGFT-OD-0910/14832, it is possible that these studies will be able to detect an increase in the rate of ATEs over the background rate.

[13] Australian Public Assessment Report for Ranibizumab (LUCENTIS), 9 November 2011, available at: <http://www.tga.gov.au/pdf/auspar/auspar-lucentis.pdf>

[14] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[15] Liao D, Mo J, Duan Y, Klein R, Scott IU, Huang KA, Zhou H. Is age-related macular degeneration associated with stroke among elderly Americans? Open Ophthalmol J 2008;2: 37-42.

Risk minimisation activities

Routine risk minimisation[16] is planned.

OPR reviewer comment

In regard to the proposed routine risk minimisation activities, the draft product information (and package insert) and consumer medicine information (CMI) are considered satisfactory. The sponsor has indicated in their response to request for information dated 24 October 2011 that additional risk minimisation activities such as physician and consumer education are not required as the proposed Australian PI covers instructions for the handling and administration of Eylea to mitigate the risks of intravitreal injection related adverse events, along with information on monitoring side effects and the CMI adequately covers potential side effects. Additional reasons provided by the sponsor include:

a) IVT injection is not a new procedure practiced by ophthalmologists in Australia as IVT administration of Lucentis has been approved for treatment of wet AMD in Australia since 2007 with a relatively low rate of IVT-related adverse events, that is,. endophthalmitis reported,

b) there is a 5 year training program and an annual continuing professional development program provided to practising ophthalmologists in Australia by the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) that cover aspects of clinical and surgical ophthalmology including intraocular injections for macular degeneration

c) RANZCO-issued practical guidelines for performing IVT therapy (August 2006)

d) RANZCO-issued information for patients on IVT procedure, potential side effects and post-IVT injection care instructions and when to seek medical attention, and

e) availability of patient education and support programs offered by the Macular Degeneration Foundation in Australia.

This was considered satisfactory, however, no information is provided in the proposed Australian PI on the recommended duration of treatment, indication for ceasing treatment or ongoing monitoring of response to treatment.

Summary of Recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application and the implementation of the Aflibercept Core Safety Risk Management Plan (CSRMP) version 2.1, 21 January 2011 and any subsequent versions, is imposed as a condition of registration.

If this submission is approved, it is recommended to the Delegate that the Sponsor:

- Includes "long-term safety" as Important missing information in the RMP.
- Updates the information provided in the CSRMP version 2.1 as per the nonclinical evaluation report.

Both of these details can be followed up administratively.

As the risk for postmarket off-label use exists based on experience with other anti-VEGF drugs, and this is unlikely to be effectively monitored by routine pharmacovigilance

[16] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

activities, it is recommended that if this submission is approved the Delegate considers the following:

- That the sponsor include "off-label use" as Important missing information in the RMP.
- That the sponsor implement additional/targeted pharmacovigilance activities to evaluate off-label use during postmarket period.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The evaluator of the quality data states that aflibercept is expressed in Chinese Hamster Ovary cells (CHO K1).

Of note in regard to the presentations, the extractable volume of 100 and 90 µL for the vial and syringe presentation, respectively, appeared to be excessive and was considered to poses a risk to patients, given that only 50 µL is required for each injection. The sponsor's reply included a suggestion that 90 µL is defined as the minimum volume that can be extracted from the syringe and that 100 µL is defined as the minimum volume that can be extracted from the vial.

Quality matters have been resolved, a shelf life of 12 months, stored at -2- 8°C, protected from light was considered approvable for both the vial and syringe presentation. A bioavailability study was not conducted, chiefly due to limitations in the assay.

As is common for biological substances, the evaluator requested samples/batch release data on the first five batches to be supplied in Australia, subject to later review. This will become a condition of registration.

Comment: The sponsor should comment on managing the risks associated with not supplying syringes and needles in the vial package and of not supplying an injection needle in the syringe pack.

Of further note, some development of the formulation occurred during the development of Eylea. As stated in the sponsor's Clinical Summary:

"During the development of VEGF Trap-Eye, the drug substance was manufactured using three different processes (IVT P1, P2 and P3). Two formulations of the drug product for IVT administration of VEGF Trap-Eye were developed and used during the clinical program: ITV-1 and ITV-2. The initial formulation ITV-1 was modified to the current ITV-2 formulation during Phase II in order to improve stability. Throughout the entire Phase III program, VEGF Trap-Eye from the same manufacturing process (IVT P3) and in the same formulation (ITV-2) was used. This formulated drug product is the same as the proposed commercial product. Table 25 below provides an overview of processes and formulations used during the whole development program."

Table 25.

Overview on manufacturing processes and formulations used during the early and late development program

Development phase	Study	Manufacturing process (drug substance)	Formulation (drug product)
Phase 1	VGFT-OD-0502	IVT P1	ITV-1
		IVT P2	ITV-1
	VGFT-OD-0603	IVT P2	ITV-1
		IVT P3	ITV-2
Phase 2	VGFT-OD-0508	IVT P2	ITV-1
	VGFT-OD-0702 long-term safety	IVT P2	ITV-1
		IVT P3	ITV-2
	VGFT-OD-0702 PK substudy	IVT P3	ITV-2
Phase 3	VIEW 1	IVT P3	ITV-2
	VIEW 2	IVT P3	ITV-2

IVT P3 is the commercial process and IVT-2 is the commercial formulation.

Nonclinical

The evaluator noted that the studies submitted were adequate in respect of toxicology and pharmacology and that they were compliant with GLP. Several species were studied; aflibercept was immunogenic in the laboratory animal species but less so in cynomolgus monkeys compared to rodents or rabbits. Monkeys were therefore used in the repeat dose toxicity studies (8 months for intravitreal injection, six months for IV injection). Specific genotoxicity and carcinogenicity studies were not submitted.

Aflibercept showed a long elimination half-life after intravitreal injection; 40 to 64 hours in cynomolgus monkeys. Aflibercept is cleared both renally and hepatically.

Animal models of efficacy (murine oxygen-induced retinopathy model; choroidal neovascularisation in the monkey (laser-induced); and normalised retinal vascular permeability in the rat (diabetic model)) supported the therapeutic concept.

The pharmacology studies' results were consistent with the purported action of aflibercept: "...as a soluble decoy receptor for vascular endothelial growth factor A (VEGF-A) and also placental growth factor 2 (PlGF-2), angiogenic ligands implicated in the pathophysiology of AMD." That is, aflibercept is expected to act as a competitive receptor of VEGF, unlike ranibizumab which is the antigen binding fragment of a humanised monoclonal antibody that binds with high affinity to the VEGF-A isoforms (such as VEGF110, VEGF121 and VEGF165), thereby preventing the binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2.

Secondary pharmacodynamic studies were conducted to exclude binding to thirty-three other human tissues or to other subtypes of VEGF (-C, -D). Aflibercept was noted to have a pressor effect in monkeys, rats and mice. Immunological studies conducted *in vitro* did not show that aflibercept can mediate complement-dependent cytotoxicity or antibody dependent cell-mediated cytotoxicity.

Toxicokinetic calculations suggest that the exposure multiples achieved in the studies were small relative to the proposed clinical dose. The relative ocular exposure was based on dose adjusted for species differences in vitreous volume; the intravitreal doses used in the pivotal monkey study (0.5, 2 and 4 mg/eye) are 0.3, 1.25 and 2.5 times the proposed human dose (2 mg/eye).

The acute toxicity of aflibercept was considered to be low. Intravitreal administration of aflibercept was followed by an anterior segment/vitreous inflammatory response in monkeys and this inflammatory response peaked at about two days after dosing. In terms of function, no angiographic or electroretinographic changes were found in treated monkeys, nor were any ocular abnormalities observed in imaging or microscopic evaluations or with intraocular pressure.

The nasal cavity was identified as the principal site of toxicity in repeat dosing, showing erosions and ulcerations of the epithelium that occurred at exposure margins ≥6 in monkeys (based on mg/kg intravitreal doses; that is, a relative exposure at the NOEL, 1.5). More extensive toxicities were seen after intravenous administration.

In brief, the toxicity studies were not extensive but adequate.

Of interest, reproduction studies suggested that fertility effects were associated with reductions in the ovarian hormones, inhibin B, oestradiol and progesterone.

Registration was supported but some product information document changes were suggested.

Clinical

The clinical trial program was compliant with Good Clinical Practice.

Pharmacokinetics

Seven studies were submitted. Unless otherwise stated, they were open-label.

Study VGFT-OD-0702 PK. See tabular description below. Efficacy data were collected and suggested greatest treatment effect at 2 mg or 4 mg per eye.

Study VGFT-OD-0603. See tabular description below. As noted by the evaluator, C_{max} occurred at 12 weeks. Mean (SE) VEGF Trap: VEGF complex concentrations at Week 12 were 0.236 (0.0302) mg/mL for ITV-1 and 0.215 (0.02) mg/mL for ITV-2.

Study VGFT-OD-0512 was a safety and tolerability study in five subjects with *diabetic macular oedema.* Aflibercept 4 mg was given as a single intravitreal injection of 100 µL volume. On Days 3 and 8, the mean concentrations of VEGF Trap were 0.0502 and 0.0272 mg/L, respectively.

Study VGFT-OD-0305 was a double masked dose escalation study, in patients with neovascular AMD, using *IV* administration (placebo, 0.3 mg/kg, 1 mg/kg, 3 mg/kg); 3 mg/kg IV was the maximal tolerated dose. C_{max} for free VEGF trap was 50 mg/L for the 3.0 mg/kg dose, around 16 mg/L for the 1.0 mg dose and 5 mg/L for the 0.3 mg/kg dose; Mean concentration to dose ratio of VEGF Trap: VEGF complex peaked at around 3.5.

Study VGFT-OD-0307 was a double-masked, placebo-controlled; sequential-group, safety, tolerability and efficacy study of aflibercept in 12 patients with *diabetic macular edema*. Only the 0.3mg/kg IV dose was studied (n=9) against placebo (n=3). After a 0.3 mg/kg dose, given IV, mean (SD) C_{max} was 600 (202) ng/mL for free aflibercept, 1522 (659) ng/mL for aflibercept : aflibercept and 1590 (699) ng/mL for total aflibercept .

Study PDY6655 is of limited pharmacokinetic relevance; it was a single-dose cross-over study in volunteers that compared subcutaneous with IV (infusion) dosing. The doses of 2.0 mg/kg were given 1 to 2 weeks apart and a carry-over effect was seen in Period 2. The volume of distribution of free VEGF Trap following IV administration was been determined to be approximately 6 L. For Period 1, for free aflibercept the mean (CV%) AUC was 177 (33) µg.day/mL and C_{max} was 44.4 (36) µg/mL for IV administration. The AUC was 84.9 (30) µg.day/mL and the C_{max} was 7.76 (39) µg/mL for subcutaneous

administration. For Period 1, for bound aflibercept the mean (CV%) AUC was 57.7 (19) µg.day/mL and the C_{max} was 1.84 (22) µg/mL for IV administration. The AUC was 47.3 (27) µg.day/mL and the C_{max} was 1.60 (27) µg/mL for subcutaneous administration. The mean (90% CI) ratio for AUC, subcutaneous/IV, was 0.51 (0.46 to 0.56).

This study also assessed safety pharmacology.

Study PDY6656 was a single centre, Phase I, randomised, double blind, placebo-controlled, sequential ascending dose study of IV aflibercept in healthy adult males that used doses of 1 mg/kg, 2 mg/kg and 4 mg/kg. There were three cohorts of 16 subjects; twelve treated with aflibercept and four treated with placebo. Pharmacodynamic endpoints were also reported.

The applicant has summarised these studies' results in the following tables (Tables 26-29).

Table 26.

Summary of Mean or Median Free VEGF Trap and Adjusted Bound VEGF Trap Exposure (AUC and C_{max}) Across Studies

Dose (unit)	Study	Route	Free VEGF Trap Mean or Median (CV%)				Adjusted bound VEGF Trap Mean or Median (CV%)			
			C_{max} mg/L	C_{max}/Dose l/L	$AUC_{0-\infty}$ day•mg/L	$AUC_{0-\infty}$ / Dose day/L	C_{max} mg/L	C_{max}/Dose l/L	$AUC_{0-\infty}$ day•mg/L	$AUC_{0-\infty}$/ Dose day/L
0.3 (mg/kg)	VGFT-OD-0305/0306 Combined PK Report	IV	4.44 (18.2)	0.233 (24.9)	11.6 (21.9)	0.548 (30.2)	0.602[a]	NA	NA	NA
1 (mg/kg)	VGFT-OD-0305/0306 Combined PK Report	IV	15.9 (19.8)	0.24 (26.2)	79.3 (28.5)	1.21 (45.6)	1.85[a]	NA	NA	NA
3 (mg/kg)	VGFT-OD-0305/0306 Combined PK Report	IV	50.5 (10.2)	0.218 (20.6)	307 (20.2)	1.16 (34.5)	NA[b]	NA	NA	NA
2 (mg/kg)	PDY6655 Period 1	IV	44.4 (36)	NA	177 (33)	NA	1.84 (22)	NA	57.7 (19)	NA
2 (mg/kg)	PDY6655 Period 2	IV	45.3 (31)	NA	181 (32)	NA	2.26 (27)	NA	76.4 (26)	NA
2 (mg/kg)	PDY6655 Period 1	SC	7.76 (39)	NA	84.9 (30)	NA	1.60 (27)	NA	47.3 (27)	NA
2 (mg/kg)	PDY6655 Period 2	SC	9.29 (32)	NA	98.4 (32)	NA	2.05 (30)	NA	69.5 (29)	NA
1 (mg/kg)	PDY6656	IV	18.2 (18)	NA	64.8 (20)	NA	1.21 (12)	NA	35.9 (11)	NA
2 (mg/kg)	PDY6656	IV	39.7 (27)	NA	180 (20)	NA	2.40 (16)	NA	72.8 (14)	NA
4 (mg/kg)	PDY6656	IV	78.6 (15)	NA	419 (21)	NA	2.72 (31)	NA	78.3 (21)	NA
2 (mg/eye)	VGFT-OD-0702.PK	IVT	0.0193 (118)	0.00965	0.153 (156)	0.0765	0.186 (40.3)	0.093	4.43 (42.3)	2.215
4 (mg/eye)	VGFT-OD-0603 ITV-1 40 mg/mL	IVT	NA	NA	NA	NA	0.331[c]	0.0828	13.4 (31.4)[d]	3.35
4 (mg/eye)	VGFT-OD-0603 ITV-2 40 mg/mL	IVT	NA	NA	NA	NA	0.239[c]	0.0598	11.7 (18)[d]	2.93
4 (mg/eye)	VGFT-OD-0603 ITV-2 80 mg/mL	IVT	NA	NA	NA	NA	0.320[c]	0.08	15.8 (27.6)[d]	3.95

Table 27.

Summary of Mean or Median VEGF Trap and Adjusted Bound VEGF Trap Exposure (AUC and C_{max}) Across Studies (Continued)

Dose (unit)	Study	Route	Free VEGF Trap Mean or Median (CV%)				Adjusted bound VEGF Trap Mean or Median (CV%)			
			C_{max} mg/L	C_{max}/Dose l/L	$AUC_{0-\infty}$ day•mg/L	$AUC_{0-\infty}$ / Dose day/L	C_{max} mg/L	C_{max}/Dose l/L	$AUC_{0-\infty}$ day•mg/L	$AUC_{0-\infty}$/ Dose day/L
0.05 (mg/eye)	VGFT-OD-0502	IVT	0	0	0	0	0	0	0	0
0.15 (mg/eye)	VGFT-OD-0502	IVT	0	0	0	0	0.02	0.13	0.41	2.73
0.5 (mg/eye)	VGFT-OD-0502	IVT	0	0	0	0	0	0	0	0
1 (mg/eye)	VGFT-OD-0502	IVT	0.01	0.01	0.03[d]	0.03	0.04	0.04	1.16[d]	1.16
2 (mg/eye)	VGFT-OD-0502	IVT	0.06	0.03	0.30[d]	0.15	0.15	0.08	6.02[d]	3.01
4 (mg/eye)	VGFT-OD-0502	IVT	0.04	0.01	0.41[d]	0.10	0.20	0.05	7.19[d]	1.80
0.5 (mg/eye)	VGFT-OD-0508	IVT	0.00084[e]	0.0017	NA	NA	0.034[f]	0.068	NA	NA
2 (mg/eye)	VGFT-OD-0508	IVT	0.0024[f]	0.0012	NA	NA	0.119[f]	0.0595	NA	NA
4 (mg/eye)	VGFT-OD-0508	IVT	0.0031[f]	0.00078	NA	NA	0.0144[f]	0.0036	NA	NA
0.5 (mg/eye)	311523 (VIEW 2)	IVT	0[a]	0	NA	NA	0.153[g,a]	0.306	NA	NA
2 (mg/eye)	311523 (VIEW 2)	IVT	0.010[a]	0.005	NA	NA	0.025[a]	0.013	NA	NA

[a] Highest reported mean concentration.
[b] Study was terminated early.
[c] $C_{trough\ max}$ value.
[d] $AUC_{0\text{-}t\text{-}last}$
[e] Dosing regimen q12w.
[f] Dosing regimen q4w.
[g] 3rd quartile used instead of arithmetic mean as one subject had a very high plasma concentration.
AUC = area under the concentration-time curve, C_{max} = maximal concentration, CV = coefficient of variation, IV = intravenous, IVT – intravitreal, NA = not assessed, SC = subcutaneous.

Table 28.

Summary of Systemic VEGF Trap Levels in Clinical AMD Studies

Study Number	Study Design	Formulation	Treatments Dose[a], Formulation	Mean Systemic VEGF Trap Levels[b] (Free and Adjusted Bound Drug Levels)					
				IVT DS Process	N[c]	Mean Free VEGF Trap[d] (range of individual results: SD)[e]		Mean Adjusted Bound VEGF Trap[f] (range of individual results: SD)	
						ng/mL	Day[g]	ng/mL	Day
VGFT-OD-0502	Phase 1, open label, dose escalation study in which six successive cohorts of patients with AMD received a single 100 µL IVT injection of 0.05, 0.15, 0.5, 1, 2, or 4 mg into the study eye; Parts A and C[h]	ITV-1	0.05 mg ITV-1 (Part A) 0.15 mg ITV-1 (Part A) 0.50 mg ITV-1 (Part A) 1 mg ITV-1 (Part A) 2 mg ITV-1 (Part A) 4 mg ITV-1 (Part A) 0.15 mg ITV-1 (Part C) 4 mg ITV-1 (Part C)	P1 P1 P1 P2 P2 P2 P1 P2	3 3 3 6 2 2 14 9	BLQ (all BLQ) BLQ (all BLQ) BLQ (all BLQ) BLQ (BLQ to 26: SD=12) 127 (86 to 168: SD=58) BLQ (BLQ to 16: SD=12) BLQ (all BLQ) 39 (BLQ to 110: SD=32)	3 3 3 3 3 3 3 3	BLQ (all BLQ) BLQ (all BLQ) BLQ (all BLQ) BLQ (BLQ to 60: SD=28) 110 (68 to 132: SD=37) 144 (101 to 188: SD=62) BLQ (BLQ to 234: SD=64) 133 (BLQ to 189: SD=48)	29 29 29 29 29 29 29 29
VGFT-OD-0508	Phase 2, double masked, prospective, randomized study in which patients with AMD received a series of 100 µL IVT injections into the study eye at 4- or 12 week intervals over a 12-week period (fixed dosing phase)	ITV-1	0.5 mg q4w ITV-1 0.5 mg q12w ITV-1 2 mg q4w ITV-1 2 mg q12w ITV-1 4 mg q12w ITV-1	P2 P2 P2 P2 P2	32 32 29 27 29	BLQ (BLQ to 18: SD=3) BLQ (BLQ to 24: SD=8) BLQ (BLQ to 39: SD=7) BLQ (all BLQ) BLQ (BLQ to 36: SD=10)	29 29 29 29 29	BLQ (BLQ to 48: SD=15) BLQ (BLQ to 54: SD=12) 68 (BLQ to 143: SD=30) 70 (BLQ to 191: SD=44) 144 (BLQ to 336: SD=75)	29 29 29 29 29

Table 29.

Summary of Systemic VEGF Trap Levels in Clinical AMD Studies (Continued)

Study Number	Study Design	Formulation	Treatments Dose, Formulation	Mean Systemic VEGF Trap Levels (Free and Adjusted Bound Drug Levels)					
				IVT DS Process	N	Mean Free VEGF Trap (range of individual results: SD)		Mean Adjusted Bound VEGF Trap (range of individual results: SD)	
						ng/mL	Day	ng/mL	Day
VGFT-OD-0603	Phase 1 study in patients with AMD comparing ITV-1 and IVT-2 formulations at 4 mg every 4 week for 12 weeks. In the double-masked cohort, patients were administered 100 µL injections of 40 mg/mL VEGF Trap-Eye. In the open-label cohort patients were administered 50 µL injections of 80 mg/mL VEGF Trap-Eye.	ITV-1 ITV-2 (40mg/mL) ITV-2 (80 mg/mL)	4 mg q4w ITV-1 (DM) 4 mg q4w ITV-2 (DM) 4 mg q4w ITV-2 (OL)	P2 P3 P3	5 5 8	BLQ (all BLQ) BLQ (all BLQ) BLQ (BLQ to 23: SD=9)	29 29 29	124 (60 to 191: SD=54) 129 (93 to 150; SD=21) 190 (52 to 296: SD=75)	29 29 29
VGFT-OD-0702 (PK Sub-study)	PK sub-study of a Phase II multi-center, open-label, extension study in which patients with AMD received a single 100 µL injection into the study Eye	ITV-2[h]	2 mg ITV-2[i]	P3	6	15.8 (BLQ to 48; SD=20)	3	149 (100 to 221; SD=47)	29

[a] Q4q4w: Dosing every 4 weeks; Q12q12w: dosing every 12 weeks
[b] Free and adjusted bound VEGF Trap levels were taken from the bioanalytical reports for the respective studies
[c] PK data not obtained for all patients at all time points
[d] Mean free VEGF Trap levels from Day 3 when available for comparisons; Day 3 is 48 hours post-dose: BLQ is <15.6 ng/mL
[e] Range of individual levels for all patients in ng/mL and standard deviation of individual results
[f] Mean adjusted bound VEGF Trap levels from Day 29 for all comparisons; Day 29 is 4 weeks post-dose; BLQ is <31.5 ng/mL
[g] For the VGFT-OD-0508 and VGFT-OD-0603 studies the first post-dost time point examined was Day 29
[h] Part B excluded because substantial PK data was available for only 1 patient
[i] All patients were initially administered the P2/ITV-1 DP in this study and later were administered the P3/ITV-2 DP; all 6 patients in the PK sub-study were administered P3/ITV-2 DP at the start of the sub-study; all patients were administered both the P2/ITV-1 and P3/IVT-2 DP during the study

In regard to pharmacokinetics in the intended treatment population, the evaluator concluded, "The systemic exposure following intravitreal injection was minimal in

comparison with studies of intravenous aflibercept. This would be expected given the differences in total dose: up to 4 mg intravitreal compared with up to 4 mg/kg intravenous."

Pharmacodynamics

Safety pharmacology

Studies PDY6655 and PDY6656 are described above. A pressor effect was seen after IV dosing. The effect was somewhat dose dependent (allowing also for the greater bioavailability of IV versus subcutaneous administration in Study PDY6656). The increase in blood pressure persisted for up to 44 days at the 4 mg/kg dose level. Plasma renin activity and aldosterone concentrations were decreased. The evaluator expressed some doubt that such an effect might be expected in regard to the proposed route of administration and dose.

Dose finding in proposed indication

Intravenous administration

"There were some Phase I data of aflibercept administered IV. *Study VGFT-OD-0305* indicated a dose of 3 mg/kg aflibercept by IV injection was effective but that a dose of 1 mg/kg was not. *Study VGFT-OD-0306* indicated that IV treatment with aflibercept would not be as effective long-term as intravitreal."

Intravitreal administration

"The Phase II study (*Study VGFT-OD-0508/14394 [CLEAR-IT AMD-2]*) did not clearly indicate the most appropriate dosing regimen. In the Phase II study the greatest reduction in CRT at Week 12 was with a 2 mg q4w dosing regimen but at all other time points over 52 weeks the greatest reduction in CRT was with 4 mg q12w. The greatest improvement in BCVA through to Week 52 was with 2 mg q4w. However the greatest improvement in vision related quality of life was with 4 mg q12w."

Study VGFT-OD-0502/14395 was an open label dose-escalation study in 21 patients with the proposed indication. The study treatments in Part A were aflibercept, given intravitreally at dose levels: 0.05 mg, 0.15 mg, 0.50 mg, 1 mg, 2 mg and 4 mg. Four outcome variables were reported. As noted by the evaluator,

"In the initial dose finding studies, the greatest effect was in the 2 mg to 4 mg dose grouping (*Study VGFT-OD-0502/14395 Part A*). Effect increased with increasing dose up to 4 mg. Peak effect appeared to be at Day 29 (Study VGFT-OD-0502/14395 Part C)." After Day 57, 9 patients continued in an open label extension to 12 months. The clinical evaluation report discussed the efficacy results at Day 57. The maximal effect was seen with a dose of 2mg or 4mg.

In *Part C of the Study*, the design was altered to double masked, randomised and the route of administration became intravitreal at doses of 0.15 mg/0.1 mL or 4 mg/0.1 mL. Fourteen patients received each dose and 22 progressed to a 12 month PRN dosing schedule at a dose of 4 mg [reported in the sponsor's summary as "Up to two injections of 0.15 or 4 mg"]. The patient population had varied indications:

Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) of 20/40 to 20/320 (73 letters to 24 letters)

Subretinal hemorrhage making up ≤ 50% of total lesion size and sparing the fovea

Total lesion size ≤12 disk area (including blood, scars, atrophy and neovascularisation) as assessed by fluorescein angiography (FA).

The higher dose was more effective. The clinical evaluation report discusses the efficacy results at Days 29 and 43.

Study VGFT-OD-0603/14396 (CLEAR-IT 1b) was evaluated but it compared two different formulations and was not a dose ranging study and it only enrolled 20 patients with a diagnosis of AMD due to active primary or recurrent subfoveal choroidal neovascularisation. Local adverse events were reported from this study.

Study VGFT-OD-0508/1494 (CLEAR-IT AMD-2) is an important study for this submission: it enrolled patients with subfoveal CNV secondary to AMD compared three intravitreal doses at 12 weekly intervals and two doses at four weekly intervals. It had one primary endpoint (retinal thickness determined by optical coherence tomography) and three secondary endpoints (including best corrected visual acuity). One hundred and fifty-seven patients received some treatment: 32 in the 0.5 mg q4w group, 32 in the 0.5 mg q12w group, 31 in the 2 mg q4w group, 31 in the 2 mg q12w group and 31 in the 4 mg q12w group. A total of 153 subjects completed to Week 12.

The dosing regimens were:

1. Aflibercept 0.5/100 µL mg every 4 weeks
2. Aflibercept 0.5/100 µL mg every 12 weeks
3. Aflibercept 2 mg/100 µL every 4 weeks
4. Aflibercept 2 mg/100 µL every 12 weeks
5. Aflibercept 4 mg/100 µL every 12 weeks

The primary outcome results were as reported in Table 10 above.

Aflibercept 2 mg/100 µL every 4 weeks and aflibercept 4 mg/100 µL every 12 weeks were associated with the best outcomes in the primary endpoint and a number of secondary endpoints. Aflibercept 2 mg/100 µL every 4 weeks was the regimen that achieved the best result in the primary endpoint at the prespecified 12 week observation. [A sample size calculation was not performed. The study did not formally compare regimens].

The evaluator questioned the rational basis for sponsor's proposed regimen (see below).

Phase III efficacy and safety studies

There were four studies of which *Study VGFT-OD-0605/14393 (VIEW 1)* and *Study 311523 (VIEW 2)* were presented as "pivotal" trials and *Studies VGFT-OD-0702/14262 and VGFT-OD-0706/13336 (DAVINCI)* were considered to be "supportive". In these studies, BCVA was chosen as the primary efficacy outcome measure in the pivotal studies. Various secondary efficacy measures, including morphological endpoints (that is, central retinal thickness (CRT) and macular volume) assessed pathology and disease severity.

Pivotal studies:

VIEW 1 and VIEW 2 were multicentric, double-masked, active-controlled, parallel-group, 2 year studies of aflibercept in the treatment of "wet" AMD. They were designed to assess the efficacy of intravitreally administered aflibercept compared to ranibizumab 0.5mg q4w, using a non-inferiority design, for preventing moderate vision loss in subjects with all subtypes of "wet" AMD. However, only the first 12 months' data were submitted with this submission. Patient exclusion criteria were extensive. Efficacy and safety evaluations were performed by a masked investigator. The untreated eye received a sham injection.

The primary efficacy endpoint was the *proportion* of subjects maintaining vision, defined as a loss of fewer than 15 letters in ETDRS letter score compared to baseline at Week 52.

VIEW 1 was conducted in the USA and in Canada. The study treatments were: Aflibercept 2 mg q4w; aflibercept 0.5 mg q4w; aflibercept 2 mg q8w or ranibizumab 0.5 mg q4w. In this study, the condition for non-inferiority was that the 95% CI for the difference in the proportion of subjects who maintained vision at Week 52 compared to baseline (ranibizumab – aflibercept) is entirely below 10%. Of note, multiplicity for the primary analysis was controlled using a conditional sequence of tests for non-inferiority: (1) aflibercept 2 mg q4w versus ranibizumab; (2) aflibercept 0.5 mg q4w versus ranibizumab; and (3) aflibercept 2 mg q8w versus ranibizumab. The study was executed above minimal patient numbers as specified in the power calculations: 1217 subjects were randomised. The treatment groups were well-matched.

The primary endpoint results at Week 52 are shown in Table 30 below.

Table 30. Proportion of Subjects who Maintained* Vision at Week 52 (Per Protocol Set)

	Ranibizumab	VEGF Trap-Eye		
	0.5Q4 (N = 269)	2Q4 (N = 285)	0.5Q4 (N = 270)	2Q8 (N = 265)
Subjects with Maintained Vision at Week 52 [1]	254 (94.4%)	271 (95.1%)	259 (95.9%)	252 (95.1%)
Difference (%) (95.1% CI) [2]				
First non-inferiority test		–0.7 (–4.4, 3.1)		
Second non-inferiority test			–1.5 (–5.1, 2.1)	
Third non-inferiority test				–0.7 (–4.5, 3.1)

[1] LOCF (baseline values were not carried forward)
[2] Difference is ranibizumab minus VEGF Trap-Eye; CI was calculated using a normal approximation.
*Maintenance of vision was defined as a loss of < 15 letters in the ETDRS letter score.

Non-inferiority was thus shown. The testing sequence stopped after the first test. However, the evaluator observed that these secondary endpoints also supported non-inferiority.

VIEW 2 was of similar design to VIEW 1 but had 126 centres in 26 countries. Sample size calculations were as for VIEW 1; 1240 patients were randomised. The treatment groups were well-matched. The primary endpoint results at Week 52 are shown in Table 31 below.

Table 31. Proportion of subjects who maintained vision at Week 52 – LOCF (per protocol set) (VIEW 2)

	Ranibizumab	VEGF Trap-Eye		
	0.5Q4 (N = 269)	2Q4 (N = 274)	0.5Q4 (N = 268)	2Q8 (N = 270)
Subjects who maintained vision at Week 52 (n [%]) [1]	254 (94.42)	262 (95.62)	258 (96.27)	258 (95.56)
Difference (%) (95% CI) [2]				
First hypothesis		-1.20 (-4.86; 2.46)		
Second hypothesis			-1.84 (-5.40; 1.71)	
Third hypothesis				-1.13 (-4.81; 2.55)

Note: Maintenance of vision was defined as a loss of < 15 letters in the ETDRS letter score
1 Last observation carried forward (Baseline values were not carried forward)
2 Difference is ranibizumab minus VEGF Trap-Eye; CI = confidence interval was calculated using a normal approximation.

Non-inferiority was thus demonstrated. As with VIEW-1, there were no significant differences between the treatment groups in the secondary efficacy outcome measures but the evaluator opined that these results were supportive of non-inferiority.

Comment: It is agreed that the three regimens of aflibercept are non-inferior in respect of the primary endpoint at 12 months, shown from VIEW-1 and in VIEW-2. The numerous secondary endpoints are harder to interpret other than qualitatively as showing small differences. Perhaps the 24 month data may show statistically significant trends in terms of the statistical plan. The Delegate noted that the sponsor pooled the 12 month data from both studies and then claim that non-inferiority has been shown in the secondary endpoints with consistency of response across various subgroups.

Supportive studies:

Study VGFT-OD-0702/14262 was conducted to compare long term safety and tolerability of aflibercept in pre-filled syringes and vials to 12 months. The aflibercept concentration was 40 mg/mL. The injection volume was 50 μL. The patients enrolled came from previous, short-term studies. The study enrolled 157 patients of whom 149 were randomised to treatment: 99 to pre-filled syringe and 50 to vial.

Visual acuity declined on study but the evaluator made no interpretive comment (see Figure 9 above).

Study VGFT-OD-0706/13336 (DAVINCI) was a study in diabetic macular oedema and is not relevant to the review of efficacy in the proposed indication. However, the study suggested that intravitreal aflibercept 2 mg q4w was more effective that 0.5 mg given at the same frequency of 4 mg given q8w or PRN.

Overall, the evaluator found:

1. The efficacy studies used validated endpoints.
2. The greatest treatment effect was with the 2 mg to 4 mg doses.
3. Effect increased with increasing dose up to 4 mg.
4. It is unclear whether a 2 mg q4w dosing regimen is therapeutically different from aflibercept 4 mg q12w as the primary endpoint in the Phase II study favoured the former regimen.
5. In the pivotal efficacy studies, non-inferiority was demonstrated for all three aflibercept dosing regimens. Secondary endpoint analyses showed variable trends.

Safety data

In addition to the abovementioned studies, safety data also derived from *Study VGFT-OD-0502/14395 Part B (CLEAR-IT 1)* and from three ongoing studies that had some limited reporting of data: *Study VGFT-OD-0910/14832, Study VGFT-OD-0819/14232 (COPERNICUS) and Study 14130 (GALILEO)*.

From the applicant's tabulation, the safety experience is limited by duration of exposure/follow-up as described in Table 32 below.

Table 32. Data pools for Safety Evaluation

	Studies	Database	Pool 1 Primary safety	Pool 2 Supportive safety	Pool 3 Exposure only
AMD	VIEW 1	up to 1 year	•		•
	VIEW 2	up to 1 year	•		•
	VGFT-OD-0502	from Week 12 up to 1 year (flexible dose regimen employed)		•	•*
	VGFT-OD-0508	from Week 12 up to 1 year (flexible dose regimen employed)		•	•*
	VGFT-OD-0603	up to 1 year		•	•
	VGFT-OD-0702	cut-off date: June 28, 2010 (pre-filled syringe versus. vial) up to 36 months			•
DME	VGFT-OD-0512	up to 6 weeks			•
	VGFT-OD-0706	up to 6 months			•
Number of subjects treated with VEGF Trap-Eye (Safety Analysis Set)			1848	230	2230

* For exposure analysis (Pool 3) single dose parts are included

Common adverse events in the pivotal studies are tabulated below (Table 33; from sponsor).

Table 33.

Most common ADRs (≥ 1 %) in Phase-3 wet AMD studies

Based on pooled data (VIEW 1 and VIEW 2)

	VEGF Trap_Eye (n= 1824)	Ranibizumab (n= 595)
Conjunctival hemorrhage	24.7%	28.1%
Eye pain	8.7%	8.9%
Cataract*	6.8%	6.6%
Vitreous detachment	6.0%	5.5%
Vitreous floaters	5.9%	7.4%
Intraocular pressure increased	5.2%	6.9%
Conjunctival hyperemia*	4.4%	7.9%
Corneal erosion*	3.7%	4.9%
Detachment of the retinal pigment epithelium	3.3%	3.4%
Injection site pain	3.0%	3.4%
Foreign body sensation in eyes	3.0%	3.7%
Lacrimation increased	2.8%	1.3%
Vision blurred	2.3%	1.8%
Retinal pigment epithelium tear	1.6%	1.2%
Injection site hemorrhage	1.5%	1.7%
Eyelid edema	1.4%	2.0%
Corneal edema	1.0%	0.5%

* MedRA labeling group terms

Source: Module 2.7.4, Table 51

The rate of patients discontinuing due to the adverse events in the studies were 2.2 % (aflibercept) and 1.1% (ranibizumab).

Shown below is the applicant's tabulation of serious adverse events from the pooled safety and efficacy studies (Table 34).

Table 34. Severe Non-Ocular Treatment-emergent AEs, Pool 1 (by SOC and PT) (Safety Analysis set).

Primary SOC Preferred term MedDRA Version 13.1	R 0.5 mg Q4 N=595	VTE 2.0 mg Q4 N=613	VTE 0.5 mg Q4 N=601	VTE 2.0 mg Q8 N=610	VTE total N=1824	TOTAL N=2419
Number of subjects with at least 1 non-ocular severe TEAE	50 (8.4%)	40 (6.5%)	59 (9.8%)	55 (9.0%)	154 (8.4%)	204 (8.4%)
Blood system and lymphatic disorders	0	1 (0.2%)	2 (0.3%)	2 (0.3%)	5 (0.3%)	5 (0.2%)
Anaemia	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	4 (0.2%)	4 (0.2%)
Haemorrhagic anaemia	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Thrombocytopenia	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Cardiac disorders	11 (1.8%)	6 (1.0%)	11 (1.8%)	14 (2.3%)	31 (1.7%)	42 (1.7%)
Acute coronary syndrome	0	1 (0.2%)	1 (0.2%)	0	2 (0.1%)	2 (<0.1%)
Acute myocardial infarction	1 (0.2%)	0	1 (0.2%)	1 (0.2%)	2 (0.1%)	3 (0.1%)
Angina pectoris	0	1 (0.2%)	1 (0.2%)	0	2 (0.1%)	2 (<0.1%)
Aortic valve stenosis	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Atrial fibrillation	2 (0.3%)	0	1 (0.2%)	3 (0.5%)	4 (0.2%)	6 (0.2%)
Bradycardia	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Cardiac arrest	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)	2 (<0.1%)
Cardiac failure	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Cardiac failure congestive	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (0.2%)	4 (0.2%)	5 (0.2%)
Coronary artery disease	4 (0.7%)	1 (0.2%)	3 (0.5%)	0	4 (0.2%)	8 (0.3%)
Coronary artery occlusion	1 (0.2%)	0	0	0	0	1 (<0.1%)
Mitral valve incompetence	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Myocardial infarction	3 (0.5%)	0	4 (0.7%)	5 (0.8%)	9 (0.5%)	12 (0.5%)
Pericarditis	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Sick sinus syndrome	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Sinus tachycardia	1 (0.2%)	0	0	0	0	1 (<0.1%)
Tachycardia	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Ventricular tachycardia	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Ear and labyrinth disorders	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Deafness unilateral	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Gastrointestinal disorders	6 (1.0%)	5 (0.8%)	5 (0.8%)	2 (0.3%)	12 (0.7%)	18 (0.7%)
Abdominal pain upper	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Colitis	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Constipation	2 (0.3%)	0	0	0	0	2 (<0.1%)
Diarrhoea	1 (0.2%)	0	2 (0.3%)	0	2 (0.1%)	3 (0.1%)
Duodenal ulcer haemorrhage	1 (0.2%)	0	0	0	0	1 (<0.1%)
Gastric ulcer	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Gastritis	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Gastritis erosive	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)	2 (<0.1%)
Gastroesophageal reflux disease	1 (0.2%)	0	0	0	0	1 (<0.1%)
Haemorrhagic erosive gastritis	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Ileus	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Intestinal obstruction	1 (0.2%)	0	0	0	0	1 (<0.1%)
Pancreatitis acute	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Tongue edema	1 (0.2%)	0	0	0	0	1 (<0.1%)
Umbilical hernia	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
General disorders and administration site conditions	4 (0.7%)	2 (0.3%)	4 (0.7%)	3 (0.5%)	9 (0.5%)	13 (0.5%)
Asthenia	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)	2 (<0.1%)
Catheter site hematoma	0	0	0	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Chest pain	2 (0.3%)	0	2 (0.3%)	0	2 (0.1%)	4 (0.2%)
Death	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Fatigue	2 (0.3%)	0	0	0	0	2 (<0.1%)
Non-cardiac chest pain	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Pyrexia	0	1 (0.2%)	0	2 (0.3%)	3 (0.2%)	3 (0.1%)
Hepatobiliary disorders	0	1 (0.2%)	2 (0.3%)	1 (0.2%)	4 (0.2%)	4 (0.2%)
Cholecystitis	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Cholelithiasis	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)	2 (<0.1%)
Hepatic cirrhosis	0	0	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Immune system disorders	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Drug hypersensitivity	0	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Infections and infestations	10 (1.7%)	5 (0.8%)	10 (1.7%)	9 (1.5%)	24 (1.3%)	34 (1.4%)
Bronchitis	0	1 (0.2%)	1 (0.2%)	0	2 (0.1%)	2 (<0.1%)
Cellulitis	0	0	2 (0.3%)	0	2 (0.1%)	2 (<0.1%)

Adverse effects of aflibercept were:

- Local, such as conjunctival haemorrhage, eye pain and reduction in visual acuity that might be associated with the injection and the vehicle; an increase in intraocular pressure of around 3.2 mmHg immediately posttreatment that did not increase with subsequent treatments [the duration of this increased intraocular pressure is not clear and the sponsor was asked to discuss the available data to substantiate the proportion that needed treatment and the time course of the increased intraocular pressure];

- Systemic adverse events after IV injection of aflibercept included headache, hypertension, proteinuria and dysphonia. Intravitreally administered aflibercept was associated with antibody formation to aflibercept in about 4% of patients in the studies;
- Serious adverse events were qualitatively similar to those expected in the population studied.

Recommendations of the clinical evaluator

An important question that the evaluator asked was,

"It is not clear from the clinical studies how the sponsor determined the final dosing recommendations in the product information document. The proposed dosing regimen (2 mg intravitreal injection each month for the first three injections followed by administration every second month) would provide the sponsor with a marketing advantage, that is, a perception that less frequent dosing is required. Hence, it is important that the dosing regimen is supported by data. Can the sponsor provide a justification for the dosing regimen proposed in the Product Information document?"

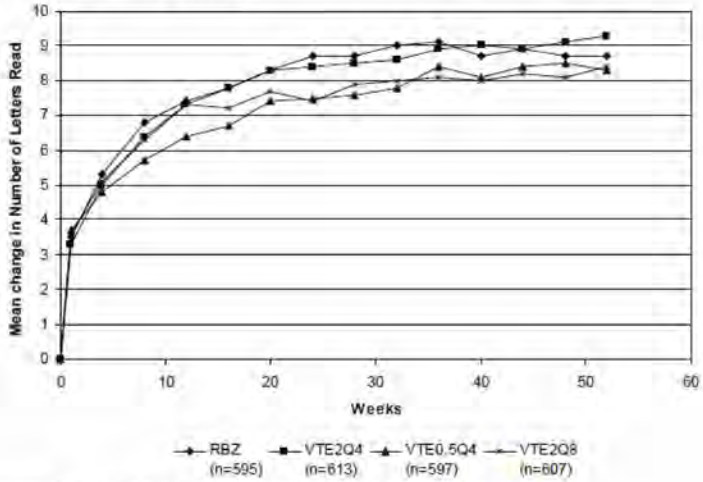
Response to the clinical evaluation report

A response has been received to the clinical evaluation report. In brief, the introduction concisely states the sponsor's position:

"The proposed dosing regimen is supported by the data presented from the Phase II study VGFT-OD-0508 and the two pivotal Phase III studies VIEW 1 and VIEW 2 and reflects the treatment advantage of a less frequent dosing scheme over a monthly dosing while efficacy as assessed by the primary endpoint is uncompromised. This is possible by the pharmacology of the product that showed the same efficacy with 2 mg q8 weeks dosing (after three initial loading doses at the start of treatment) as with 2 mg q4 weeks dosing consistently in both pivotal studies. The efficacy of either regimen of VEGF Trap Eye was compared to monthly dosing of the reference product ranibizumab and was found non-inferior in the primary endpoint and can be considered clinically equivalent. Generally, as there are additional risks and burdens associated with a q4 regimen compared with a q8 regimen, the q8 regimen was judged to have a better benefit/risk profile. Therewith, dosing of VEGF Trap-Eye every two months (after three initial loading doses at start of treatment) is justified as it constitutes a good benefit/risk ratio supporting marketing authorisation. The dosing every two months allows also for reducing the number of frequent visits and reduces the general potentially serious risks associated with frequent intravitreal injections without compromising efficacy."

That is, safety concerns are used to support less frequent dosing. However, the Phase II study had small numbers in each treatment arm and could not be used to make robust conclusions; it is possible to make alternative interpretation, as shown below (Figure 11).

Figure 11. Integrated Analysis of the pooled data from the pivotal studies-Mean change in BCVA (FAS, LOCF).



Source: Module 5.3.5.3 Integrated Analysis Pool 1 Table 1.2.2/1
FAS=Full Analysis Set

The figure shows a trend to better results for 4 weekly injections and not 8 weekly. The response does not cite study data that show a higher rate of local adverse events attributable to more frequent injections, so this suggestion by the sponsor is taken to be "in principle".

Comments

The use of OCT as a primary endpoint was probably useful as an objective tool research but best corrected visual acuity might be more clinically practical. VIEW-1 and VIEW-2 used an appropriate primary endpoint.

The dosing regimen of ranibizumab that was used in the two pivotal studies was acceptable, indeed a little high in terms of drug exposure.

An emerging safety issue with ranibizumab has been the correct dose selection and choosing the right dose (for example, is 0.5 mg too much?) and establishing the longest dosing interval that is compatible with an optimal treatment effect. This matter has not yet been resolved but the current product information document of Lucentis includes the following information:

*"**Treatment of Wet AMD***

The recommended dose of Lucentis is 0.5 mg (0.05 mL) or 0.3 mg (0.03 mL) given as a single intravitreal injection.

Lucentis is given monthly. The interval between two doses should not be shorter than 1 month. Although less effective, treatment might be reduced to one injection every 3 months after the first three injections (e.g. if monthly injections are not feasible) but, compared to continued monthly doses, dosing every 3 months may lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following nine months. Patients should be evaluated regularly.

Post-Registration Study in DME population

An analysis of 24-month data from two Phase III studies in DME, RIDE and RISE, is available. Both studies are randomised, sham-controlled studies of monthly intravitreal ranibizumab injections (0.5 mg or 0.3 mg) for a total of 36 months in patients with clinically significant macular oedema with centre involvement secondary to diabetes mellitus (Type 1 or Type 2).

The patients are treated using a fixed dosing regimen which requires monthly injections as opposed to the approved individualised dosing regimen (see Dosage and Administration). A total of 500 patients were exposed to ranibizumab treatment in the pooled studies (250 patients in each pooled ranibizumab 0.3mg and 0.5mg arm as well as the sham arm.

The pooled safety analysis showed a numerically higher, but not statistically significant, number of deaths and cerebrovascular events in the 0.5 mg group as compared to the 0.3 mg or sham groups. The stroke rate at 2 years was 3.2% (8/250) with 0.5 mg ranibizumab, 1.2% (3/250) with 0.3 mg ranibizumab, and 1.6% (4/250) with sham. Fatalities in the first 2 years occurred in 4.4% (11/250) of patients treated with 0.5mg ranibizumab, in 2.8% (7/250) of patients treated with 0.3 mg ranibizumab and in 1.2% (3/250) of control patients."

Risk management plan

In regard to the status of Eylea abroad, the evaluator has noted:

"Eylea was approved by the US FDA on 18 November 2011 for the same indication as those proposed for in Australia. A postmarketing pharmacovigilance requirement has been imposed by the FDA for a clinical trial to be conducted to assess the risk of unexpected serious adverse events for Eylea, specifically for corneal endothelial cell decompensation."

"Endophthalmitis is identified as an important injection-related safety concern while arterial thromboembolic events (ATEs) and embryo-fetal toxicity are identified as potential drug related safety concerns. It is proposed that routine pharmacovigilance (PhV) is supplemented by targeted follow-up of reports of suspicious of intraocular infection. Data from the ongoing clinical trial programme will provide additional monitoring and characterization of the safety profile of aflibercept. Routine risk minimisation is proposed for the ongoing safety concerns."

Safety data in patients are limited by numbers and duration (52 weeks in Phase III trials). Ongoing safety concerns in the safety specification of the Risk Management Plan include at this time a lack of available long-term data; ongoing studies are noted but the sponsor's claim of comparable safety with Lucentis has not been established in terms of duration of experience. Further data will accrue from clinical trials that are in progress.

The evaluator has noted the potential for overdose from both presentations but not, for example, the potential risk of multipatient use by combining the residual amount in several vials. Other concerns include use in unapproved indications; the lack of clarity in the draft product information document about experience in long term use; and an open question about the prophylactic use of antibiotic eye drops to reduce the risk of endophthalmitis.

The latest version of the risk management has not been fully accepted by the evaluator. The applicant was asked to address this in the pre Advisory Committee on Prescription Medicines (ACPM) response.

Risk-benefit analysis

Delegate considerations

Comments on this application

The application is supported by an adequate data package in respect of quality and nonclinical matters.

The nonclinical studies, particularly those conducted in cynomolgus monkeys, are informative in regard to local toxicity.

The use of Lucentis as an active comparator in the clinical studies is ethically necessary. Lucentis was given at a high dose and adequate frequency, so ensuring that Eylea was not advantaged in the comparison. Combined use of these agents is unlikely to be of benefit and there are no data on the use of aflibercept in patients who fail to respond to ranibizumab.

Theoretically, the use of aflibercept in combination with a second agent such as anecortave or a corticosteroid would be of value in some potential indications but there are no such studies.

The risk management activities that are planned were considered reasonable.

The PI document should make it clear that there are no evaluated data beyond 12 months and that the optimal dosing schedule has not been defined.

The ACPM was asked to comment on these matters.

Proposed actions

The application by Bayer Australia Limited to register Eylea solution for intravitreal injection, containing aflibercept (solution) at 2 mg aflibercept per 50 µL, for the treatment of neovascular (wet) age-related macular degeneration (AMD) should be approved.

Bayer Australia Limited should submit for evaluation the completed pivotal studies. It was noted that this application was based on 12month, not 24 month data.

Submitted for ACPM's advice.

Response from sponsor

The TGA Evaluators (for quality, nonclinical, clinical, risk management plan [RMP] aspects) and the Delegate have all recommended that Eylea should be approved for the treatment of wet AMD. Overall, the sponsor is in agreement with the TGA Evaluators and Delegate that the efficacy of Eylea has been conclusively demonstrated in two pivotal Phase III clinical studies (VIEW 1 + VIEW 2) and the overall safety profile is favourable such that Eylea is registrable based on these data. The benefit-risk assessment is positive for Eylea and, furthermore, the dosing regimen of every 2 months, after 3 initial loading doses at the start of treatment provides additional potential benefit over current therapies in patients with wet AMD. However, in this response, the sponsor wishes to provide further comments and clarifications to the Delegate's Overview.

The Delegate commented that the product information should make it clear that there are no evaluated data beyond 12 months and that the optimal dosing schedule has not been defined.

The sponsor contended that the clinical trial section of the PI already clearly states that the efficacy outcomes presented in support of Eylea and the proposed dosing schedule are based on the primary analyses conducted at 12 months. Therefore, the sponsor does not believe that any further clarification is needed in the PI regarding this point.

The VIEW 1 and VIEW 2 studies have now reached their full course and the results at 96 weeks continued to support the positive benefit-risk assessment made based on the primary analyses at Week 52.

The sponsor believes that the optimal dosing schedule of 2 mg Eylea every 8 weeks (2q8) following 3 initial monthly doses is fully supported by the efficacy and safety results from the pivotal Phase-3 studies, VIEW 1 and VIEW 2, and the integrated analysis of the data from these studies. The pivotal studies show that a 2q8 dosing regimen provides equivalent efficacy, especially in regard to the most clinically important outcome, visual acuity, as a monthly dosing regimen of the currently approved treatment for wet AMD. The requirement for less frequent dosing with Eylea from an efficacy perspective is clearly

supported by the clinical data submitted. In addition, review of the data from the 2q8 group did not reveal clinically relevant changes in the efficacy variables between injections. These findings support the conclusion that there is no need for monitoring patients more frequently than every 2 months as no decreases in efficacy that would prompt retreatment were seen between active injections spaced 2 months apart.

In regard to patient safety, because of the safety issues inherent with the application of intravitreal injections (that is, each injection carries the risk for an adverse event), it is in the best interest of the patient to maintain visual acuity and quality of life with the minimal number of injections as possible (and thereby minimum opportunity for an adverse event) without compromising efficacy.

Finally, a reduction in the number of clinic visits without the need for monitoring between visits and no concern for deterioration of visual acuity, also alleviates much of the burden to patients and caregivers and frees up provider resources. The current gold standard treatment for exudative AMD involves monthly injections of Lucentis. However, this regimen places considerable treatment burden and costs on patients and workload for clinicians. Therefore, many ophthalmologists have implemented a treatment regimen that requires fewer injections than the Lucentis approved label by using either the "as needed" (that is, PRN) or "inject & extend" approach. These major barriers to treatment will be met with the introduction of Eylea, which will offer a new, fixed-dosing regimen of bimonthly injections (after 3 initial loading doses at the start of treatment).

In conclusion, fewer doses of Eylea are needed to achieve the same efficacy as monthly dosing with Lucentis and indeed, the data do not support that more frequent dosing with Eylea or more frequent monitoring of patients results in a better clinical outcome than dosing (and monitoring) every 8 weeks. It is self-evident that, given equivalent clinical efficacy, a regimen with fewer intravitreal injections and fewer monitoring visits to the clinic is preferable to one with more intravitreal injections and more visits. Therefore, based on positive considerations of efficacy, safety, and impact on patient and caregiver, the sponsor recommends the optimal dosing regimen of initiating treatment with 2 mg intravitreal injection each month for 3 consecutive months followed by administration of 2 mg every 2 months.

The Delegate commented that safety concerns are used to support less frequent dosing but the Phase II Study VGFT-OD-0508 had small numbers in each treatment arm and could not be used to make robust conclusions and that it is possible to make alternative interpretation.

The sponsor based the recommended dosing regimen, 2 mg every 8 weeks after 3 initial monthly doses, primarily on the efficacy results of the pivotal Phase III studies, which showed no clinically relevant difference in the efficacy achieved with dosing every 4 weeks versus dosing every 8 weeks. In other words, more frequent injections do not result in greater efficacy. There is a low, but defined, per-injection incidence of complications associated with the intravitreal injection procedure. Based on logical considerations that fewer injections, each of which carries risk for an adverse event, expose the patient to fewer opportunities for an adverse event, the sponsor believes that Eylea may impart a clinically relevant decrease in the risk of serious complications associated with intravitreal injections without compromising benefit to the patient.

With reference to the figure representing integrated analysis of pooled data from the pivotal studies for mean change in BCVA, the Delegate commented that the graph shows a trend to better results for 4 weekly injections and not 8 weekly.

The sponsor clarified that the figure representing the integrated analysis of pooled data from the pivotal studies for mean change in BCVA shows a change from baseline at Week 52 of 9.3 ± 13.3 letters in the Eylea 2Q4 (2 mg every 4 weeks) group and 8.4 ± 14.7 letters in the Eylea 2Q8 (2 mg every 8 weeks) group. In the VIEW 1 study, the change from

baseline at Week 52 was 10.9 ± 13.77 letters and 7.9 ± 15.00 letters in these two Eylea groups, respectively, and in VIEW 2, 7.6 ± 12.6 letters vs. 8.9 ± 14.4 letters, respectively. The sponsor does not consider the observed difference between treatment groups to be of clinical relevance in the context of the studies as a whole and, therefore, stands behind the conclusion that 2 mg Eylea dosed every 8 weeks provides the same efficacy as when dosed every 4 weeks. Minor differences seen between treatment groups in the clinical studies represent random variability and not a clinically meaningful outcome.

The Delegate commented that the sponsor's justification for the proposed dosing regimen does not cite study data that show a higher rate of local adverse events attributable to more frequent injections and so the sponsor's suggestion is taken to be "in principle".

The sponsor acknowledged that this part of the justification is indeed proposed "in principle" because (1) the pivotal studies were not designed (that is, not powered) to show differences in the incidence of adverse events and (2) although subjects in the 2q8 group received fewer "real" injections, they underwent all the same preparatory procedures and a sham injection, which included touching and applying pressure to the eye. Based on logical considerations that fewer injections, each of which carries risk for an adverse event, expose the patient to fewer opportunities for an adverse event, the sponsor believes that Eylea may impart a clinically relevant decrease in the risk of serious complications associated with intravitreal injections. This reduction of risk is by virtue of the bimonthly treatment regimen with Eylea such that the number of injections given over the first year in a 2q8 dosing regimen is reduced by more than 40% compared to monthly treatment and therefore, the risk of any injection-related adverse event, including serious complications such as endophthalmitis, may also be reduced by a similar magnitude.

The Delegate acknowledged that the three regimens of aflibercept are non-inferior in respect of the primary endpoint at 12 months in VIEW 1 and VIEW 2 but commented that the numerous secondary endpoints are harder to interpret, other than qualitatively as showing small differences. The Delegate suggested that perhaps the 24 month data may show statistically significant trends in terms of the statistical plan, noting that the 12 month data was pooled from both studies to support a claim for non-inferiority in the secondary endpoints with consistency or response across various subgroups.

The sponsor clarified that no claim of non-inferiority was made based on the secondary efficacy endpoints.

The VIEW 1 and VIEW 2 studies included four secondary endpoints: change from baseline in BCVA as measured by ETDRS letter score at Week 52, proportion of subjects who gained at least 15 letters of vision from baseline to Week 52, change in total NEI VFQ-25 score from baseline to Week 52, and change in CNV area from baseline to Week 52. All other endpoints were considered to be exploratory and were not subjected to formal statistical analysis. In addition, based on the conditional sequence of statistical hypothesis tests, which controlled for multiplicity in the testing of these four secondary endpoints, the hierarchical testing had to be stopped after the first or second step, because the pairwise comparison failed to show a statistically significant treatment difference between the Eylea 2q4 group and the Lucentis 0.5q4 (0.5 mg every 4 weeks) group. Therefore, the p-values provided for all subsequent steps were for descriptive purposes only and were not used to make a claim of superiority. Regarding the secondary efficacy endpoints, based on the confidence intervals for the differences between Lucentis and Eylea, both studies concluded that all secondary endpoint analyses supported the comparability of the efficacy of Lucentis and all 3 Eylea treatment schedules, including the 2 mg bimonthly regimen.

The pooled efficacy data from Year 1 are presented in the sponsor's Summary of Clinical Efficacy. There is no mention in this document that non-inferiority has been shown in the secondary endpoints. The only mention of non-inferiority is made in reference to the primary endpoint, proportions of subjects who maintained vision at Week 52.

The sponsor clarified further that all primary and secondary endpoint analyses performed on the Year 1 data were repeated for the data covering the whole 2 year study period and all such analyses were considered to be only exploratory in nature.

With respect to safety data and the observed increase in intraocular pressure of around 3.2 mmHg immediately post-treatment that did not increase with subsequent treatments, the Delegate requested clarification around the duration of this increase in intraocular pressure, the proportion that needed treatment and the time course of the increased intraocular pressure.

The sponsor clarified that a transient increase in intraocular pressure (IOP) immediately post-injection is an expected event with any intravitreal injection. There is no suggestion in the data from the pivotal studies that Eylea is associated with an excessive or durable increase in IOP, as evidenced by the subsequent IOP. No mean increases in pre-dose IOP occurred in any treatment group during the first year of treatment. Increases in IOP were reported as treatment-emergent adverse events at a lower incidence with Eylea (5.2%) than Lucentis (6.9%) and in both treatments, most were considered to be related to the injection procedure (Eylea 3.2%; Lucentis 4.5%) and not the study drug (Eylea 0.5%; Lucentis 1.2%). In subjects with "sustained" increases in IOP, defined as consecutive visits with pre-injection IOP > 21 mmHg or ≥ 25 mmHg, more subjects treated with Lucentis met this definition than those treated with Eylea. This was true for both the study eye as well as the non-injected fellow eye.

The single subject (in the Eylea 2q8 group) who discontinued the study because of an TEAE of IOP increased experienced two non-serious, mild events of IOP increased, once to 28 mmHg and once to 29 mmHg. In both instances the study drug was temporarily withdrawn and the subject recovered. The investigator did not consider the events to be related to study drug or study procedures.

Overall, the need for IOP-lowering interventions with the exception of the routine prophylactic use of IOP lowering medications at some study sites, did not suggest that many subjects in these studies were developing ocular hypertension. IOP increased is listed as an adverse drug reaction (ADR) for the product and, therefore, is adequately handled in the product labelling with regard to patient safety.

In relation to the proposed RMP, the Delegate acknowledged that the planned risk management activities are reasonable but commented that the risk management plan has not been fully accepted by the evaluator.

The sponsor clarified and drew TGA's and ACPM's attention to their response of 24 October 2011, which answered the quality evaluator's question surrounding the potential for overdose from the PFS and vial presentations. The potential risk of multi-patient use by combining residual amounts from several vials is considered to be very low. Given that there is little to no meaningful amount of residual volume following withdrawal of the content to prepare the 50 µL dose, it would be very difficult, if not impossible, to combine the residual contents of multiple vials to obtain a usable volume of the product. As reinforced in the PI, administration must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. The PI clearly instructs that each pre-filled syringe or vial should only be used for the treatment of a single eye and that any unused product must be discarded following injection.

The Delegate requested the sponsor to comment on managing the risks associated with not supplying syringes and needles in the vial package and not supplying an injection needle in the syringe pack.

The sponsor believes that injection needles, available from various existing suppliers, would be readily available to the experienced physicians administering Eylea and acknowledges that practicing ophthalmologists often prefer one brand of injection needle over another. Not including an injection needle in the packaging for Eylea therefore provides flexibility to the physician and allows him/her to use the brand with which he/she has the most experience. The PI recommends a 30-G ½- inch injection needle for the administration of Eylea, although there is no risk from using a needle of a slightly different size as long as such a needle was selected based on the experience and standards of the qualified treating physician.

In the event that the vial presentation is marketed, a filter fill needle would be supplied in the packaging as a filter needle may not be readily available to a treating physician. As is the case with the injection needle, the sponsor believes that appropriate syringes, available from various existing suppliers would be readily available to the experienced physicians administering Eylea and therefore, inclusion of a syringe in the vial packaging is not necessary.

Advisory committee considerations

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

The ACPM considered this product to have a positive benefit-risk profile for the indication;

For the treatment of neovascular (wet) age-related macular degeneration (AMD).

In making this recommendation, the ACPM considered the dosage regimen, as proposed by the sponsor was appropriate.

The ACPM supported the amendments proposed by the Delegate to the Product Information (PI) and Consumer Medicines Information (CMI) and others which should be considered include;

- a statement in the *Dosage and Administration / Clinical Trial* sections to highlight the absence of evaluated data beyond 12 months of use.
- the reporting of the primary endpoint for each of the two pivotal studies should be the main focus of statements in the *Clinical Trials* section. The secondary endpoints for each study may be listed and, where relevant, described as favourable trends but the statistical limitations should be disclosed. The fact that the studies are planned to run for two years should also be disclosed.

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

Outcome

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

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

Specific conditions applying to these therapeutic goods:

1. The implementation in Australia of the Eylea (aflibercept) 40 mg/mL solution for intravitreal injection (pre-filled syringe and vial) Risk Management Plan (RMP), dated 21 January 2012 included with the submission and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

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

PRODUCT INFORMATION

EYLEA®
aflibercept (rch)

NAME OF THE MEDICINE

Active ingredient:	Aflibercept
Chemical names:	Vascular endothelial growth factor receptor type VEGFR-1 (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer
CAS number:	862111-32-8
Molecular weight:	97 kDa (protein molecular weight) 115 kDa (total molecular weight)
Structure:	The secondary and tertiary structures of aflibercept as well as the amino acid structure are shown in Figures 1 and 2.

Figure 1: Aflibercept secondary and tertiary structures

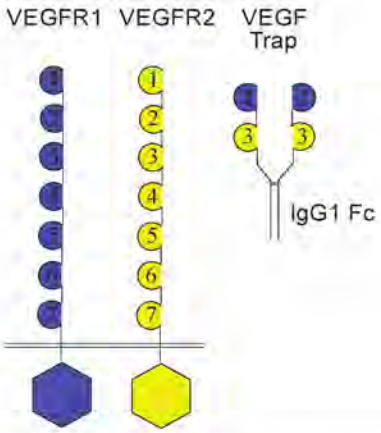
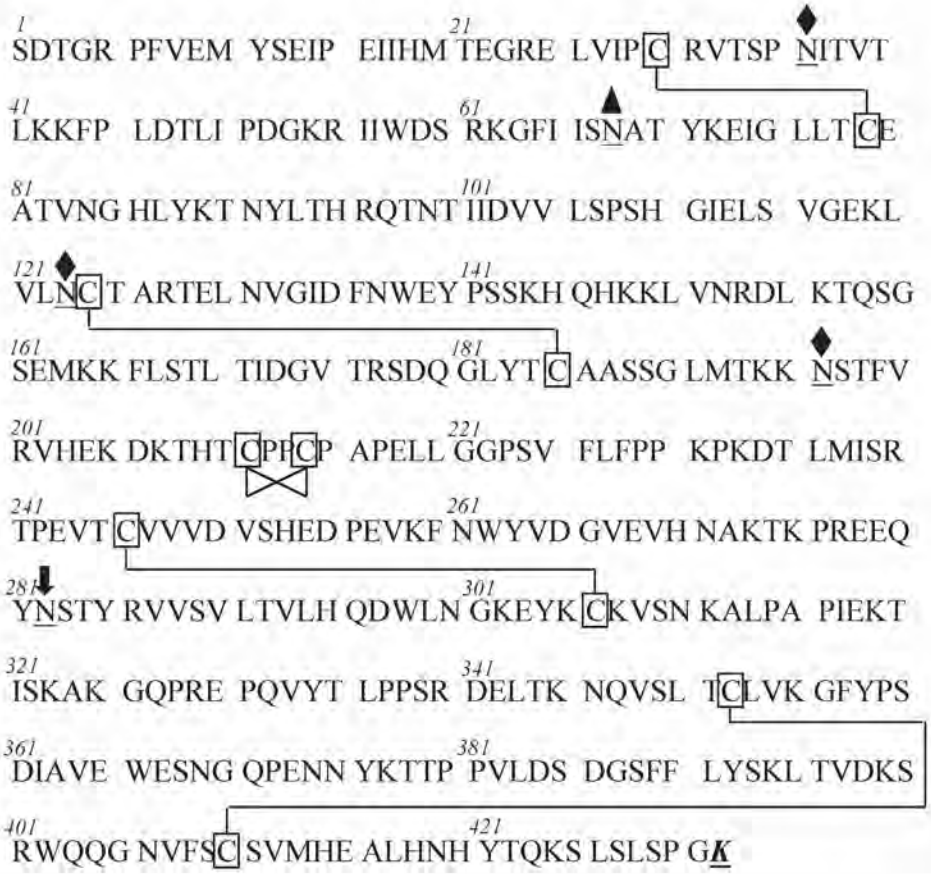


Figure 2: Aflibercept amino acid structure



DESCRIPTION

EYLEA is a sterile, clear, colourless to pale yellow, preservative-free, iso-osmotic aqueous 40 mg/mL solution for intravitreal injection.

Excipients: Polysorbate 20, sodium phosphate - monobasic monohydrate, sodium phosphate - dibasic heptahydrate, sodium chloride, sucrose, water for injection.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals / Antineovascularization agents

ATC Code: S01LA05

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

Mechanism of action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leukocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergise with VEGF-A in these processes, and is also known to promote leukocyte infiltration and vascular inflammation. A variety of ocular diseases, including neovascular (wet) age-related macular degeneration (AMD), are associated with pathologic neovascularisation and vascular leakage, and can result in thickening and oedema of the retina, which is thought to contribute to vision loss.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. The equilibrium dissociation constant (K_D) for aflibercept binding to human VEGF-A_{165} is 0.5 pM and to human VEGF-A_{121} is 0.36 pM. The K_D for binding to human PlGF-2 is 39 pM.

Pharmacodynamic effects

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

In patients treated with EYLEA (one injection per month for three consecutive months, followed by one injection every 2 months), retinal thickness decreased soon after treatment initiation, and the mean CNV lesion size was reduced, consistent with the results seen with ranibizumab 0.5 mg every month.

In pivotal phase III clinical studies, VIEW 1 and VIEW 2, there were mean decreases in retinal thickness on optical coherence tomography (OCT) at week 52: -130 and -129 microns for the EYLEA 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively, in VIEW 1; -149 and -139 microns for the EYLEA 2 mg every two months, and ranibizumab 0.5 mg every month study groups, respectively, in VIEW 2.

Pharmacokinetic properties

EYLEA is administered directly into the vitreous to exert local effects in the eye.

Absorption / Distribution

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

In a pharmacokinetic sub-study with frequent sampling, maximum plasma concentrations of free aflibercept (systemic C_{max}) were low, with a mean of approximately 0.02 µg/mL (range 0 to 0.054) within 1 to 3 days after 2 mg intravitreal injection, and were undetectable two weeks following dosage in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks.

The mean maximum plasma concentration of free aflibercept is approximately 50 to 500 times below the aflibercept concentration required to inhibit the biologic activity of systemic VEGF by 50% in animal models. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF. Therefore, systemic pharmacodynamic effects are unlikely.

Elimination

As EYLEA is a protein-based therapeutic, no metabolism studies have been conducted.

Free aflibercept binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism.

Patients with renal impairment

No special studies in patients with renal impairment were conducted with EYLEA. Pharmacokinetic analysis of patients in the VIEW 2 study, of which 40% had renal impairment (24% mild, 15% moderate, and 1% severe), revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 or 8 weeks.

CLINICAL TRIALS

The safety and efficacy of EYLEA were assessed in two pivotal phase III randomised, multi-centre, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW 1 and VIEW 2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

1. EYLEA administered at 2 mg every 8 weeks (EYLEA 2Q8) following 3 initial monthly doses
2. EYLEA administered at 2 mg every 4 weeks (EYLEA 2Q4)
3. EYLEA administered at 0.5 mg every 4 weeks (EYLEA 0.5Q4)
4. Ranibizumab administered at 0.5 mg every 4 weeks (Ranibizumab 0.5Q4)

Patient ages ranged from 49 to 99 years with a mean of 76 years. Approximately 89% (1616/1817) of the patients randomised to treatment with EYLEA were 65 years of age or older and approximately 63% (1139/1817) were 75 years of age or older.

Primary efficacy data at 52 weeks have been evaluated for these studies that are planned to run for 96 weeks.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. The studies were intended to test for non-inferiority against ranibizumab 0.5 mg given every 4 weeks.

In the VIEW 1 study, at week 52, 95.1% of patients in the EYLEA 2Q8 treatment group maintained vision compared to 94.4% of patients in the ranibizumab 0.5Q4 group. EYLEA treatment was shown to be non-inferior to the ranibizumab 0.5Q4 group.

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

The VIEW 1 and VIEW 2 studies included four secondary efficacy endpoints: mean change in Best Corrected Visual Acuity (BCVA), proportion of patients who gained ≥15 letters, change in the total National Eye Institute Visual Function Questionnaire (NEI VFQ-25) score, and change in CNV area.

Detailed results from the combined analysis of both studies (primary* and secondary# endpoints) are shown in Table 1 and Figure 3 below.

Table 1: Efficacy outcomes at week 52; combined data from the VIEW 1 and VIEW 2 studies (b)

Efficacy outcome	**EYLEA 2 mg Q8 (e) (n = 607)**	**Ranibizumab 0.5 mg Q4 (n = 595)**
Mean number of active injections over 52 weeks	7.6	12.3
Proportion of patients with maintained visual acuity (<15 letters of BCVA (a) loss) (Per Protocol Set) *	95.33%	94.42%
Difference (c) (95% CI) (d)	0.9% (-1.7, 3.5)(f)	N/A
Mean change in BCVA as measured by ETDRS (a) letter score from baseline #	8.40	8.74
Difference in LS (a) mean (ETDRS letters) (c) (95% CI) (d)	-0.32 (-1.87, 1.23)	N/A
Proportion of patients who gained at least 15 letters of vision from baseline #	30.97%	32.44%
Difference (c) (95% CI) (d)	-1.5% (-6.8, 3.8)	N/A
Mean change in total score as measured by NEI VFQ-25 from baseline #	5.00	5.56
Difference in LS (a) mean (NEI VFQ-25 score) (c) (95% CI) (d)	-1.26 (-2.72, 0.20)	N/A
Mean change in CNV area as measured by FA (a) from baseline #	-4.28	-4.21
Difference in LS (a) mean (CNV area) (g) (95% CI) (d)	0.08 (-0.46, 0.61)	N/A

(a) BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LS mean: least squares mean
FA: Fluorescein angiography

(b) Full Analysis Set (FAS), Last Observation Carried Forward (LOCF); only proportion of patients with maintained visual acuity is shown for the Per Protocol Set (PPS)

(c) The difference is the value of the EYLEA group minus the value of the ranibizumab group. A positive value favours EYLEA.

(d) Confidence Interval (CI) calculated by normal approximation

(e) After treatment initiation with three monthly doses

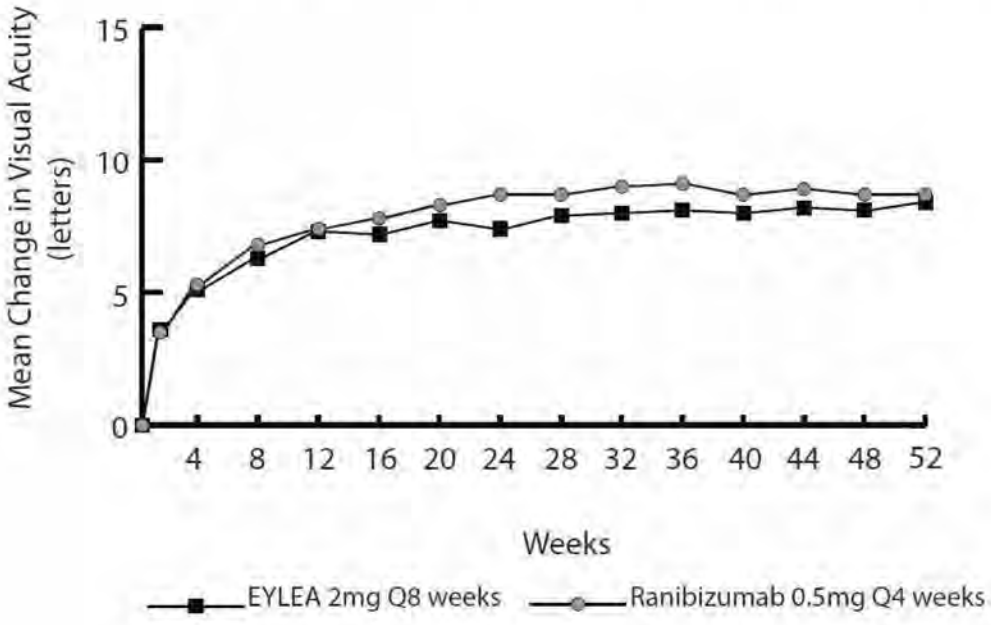
(f) A confidence interval lying entirely above -10% indicates a non-inferiority of EYLEA to ranibizumab

(g) The difference is the value of the EYLEA group minus the value of the ranibizumab group

* Primary endpoint

\# Secondary endpoint – see statistical comment below

Figure 3: Mean change in visual acuity from baseline to week 52[#]; combined data from the VIEW1 and VIEW2 studies



While there were small differences between EYLEA and ranibizumab, no clinically relevant differences were seen between the treatment groups across all four secondary efficacy endpoints, based on the confidence intervals for the differences between EYLEA and ranibizumab. All statistical tests on secondary efficacy endpoints were considered to be exploratory in the combined analysis of both studies. All secondary endpoint analyses supported the comparability of the efficacy of all 3 EYLEA treatment schedules and ranibizumab.

In combined data analysis of the VIEW 1 and VIEW 2 studies EYLEA demonstrated clinically meaningful changes from baseline in NEI VFQ-25 scores and subscales (near activities, distance activities, and vision-specific dependency). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in BCVA.

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

INDICATIONS

EYLEA (aflibercept) is indicated for the treatment of neovascular (wet) age-related macular degeneration (wet AMD).

CONTRAINDICATIONS

- Known hypersensitivity to aflibercept or to any of the excipients
- Ocular or periocular infection
- Active severe intraocular inflammation

PRECAUTIONS

Endophthalmitis

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis (see **ADVERSE EFFECTS**). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay and should be managed appropriately.

Increase in intraocular pressure

Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection, including with EYLEA (see **ADVERSE EFFECTS**). Special precaution is needed in patients with poorly controlled glaucoma. In all cases both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.

Effects on fertility

Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg every one to two weeks. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility (considered consequential to male fertility) were observed at all dose levels. Based on C_{max} and AUC for free aflibercept observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 4900-fold and 1500-fold higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

Use in pregnancy (Category D)

There are no data on the use of aflibercept in pregnant women. Studies in animals have shown reproductive toxicity, including a series of external, visceral, skeletal malformations, after systemic administration. EYLEA is not recommended during pregnancy unless the potential benefit outweighs the potential risk to the fetus. Women of childbearing potential should use effective contraception during treatment.

Aflibercept produced malformations and other fetal abnormalities in pregnant rabbits with intravenous administration (at 3 to 60 mg/kg once every 3 days during the period of organogenesis). A No Observed Effect Level (NOEL) for adverse effects on embryofetal

development was not established. At the lowest dose tested (3 mg/kg), the systemic exposures based on C_{max} and AUC for free aflibercept were approximately 2900-fold and 600-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.

Use in lactation

It is unknown whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded. EYLEA is not recommended during breast-feeding. A decision must be made whether to discontinue breast-feeding or to abstain from EYLEA therapy.

Paediatric use

Wet AMD does not occur in children and adolescents. Therefore the safety and efficacy of EYLEA have not been studied in these age groups.

Use in the elderly

No special considerations are needed.

Genotoxicity

No studies have been conducted on the mutagenic or clastogenic potential of aflibercept. As a large protein molecule, aflibercept is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

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

Effects on ability to drive or use machines

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. They should not drive or use machinery until visual function has recovered sufficiently.

INTERACTIONS WITH OTHER MEDICINES

No formal drug interaction studies have been performed with EYLEA.

ADVERSE EFFECTS

A total of 1824 patients constituted the safety population in the two phase III studies with up to 96 weeks of exposure to EYLEA, and 1223 patients were treated with the 2 mg dose.

Summary of the safety profile

Serious adverse reactions related to the injection procedure have occurred in less than 1 in 1,000 intravitreal injections with EYLEA and included endophthalmitis, traumatic cataract and transient increased intraocular pressure (see **PRECAUTIONS**).

The most common adverse reactions (in at least 5% of patients treated with EYLEA) were conjunctival haemorrhage (26.7%), cataract (12.8%), eye pain (10.3%), vitreous detachment (8.4%), vitreous floaters (7.6%), and increased intraocular pressure (7.2%). These adverse reactions occurred with a similar incidence in the ranibizumab treatment group.

Tabulated list of adverse reactions

The safety data described below include all adverse reactions (serious and non-serious) with a reasonable possibility of causality to the injection procedure or medicinal product over the 96 weeks study duration.

The adverse reactions are listed by system organ class and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100).

Table 2: Adverse reactions in phase III wet AMD studies

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Eye disorders	Cataract, Conjunctival haemorrhage, Eye pain	Retinal detachment, Retinal pigment epithelium tear, Detachment of the retinal pigment epithelium, Corneal erosion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Corneal oedema,	Endophthalmitis, Retinal tear

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
		Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Conjunctival hyperaemia	
Immune system disorders			Hypersensitivity

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

ATEs, as defined by Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause). The incidence in the VIEW 1 and VIEW 2 wet AMD studies during the 96 weeks study period was 3.3% (61 out of 1824) in the combined group of patients treated with EYLEA compared with 3.2% (19 out of 595) in patients treated with ranibizumab.

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

DOSAGE AND ADMINISTRATION

EYLEA is for intravitreal injection only.

It must only be administered by a qualified physician experienced in administering intravitreal injections.

Dosage regimen

The injection volume is 50 μL of EYLEA (equivalent to 2 mg aflibercept).

EYLEA treatment is initiated with one injection per month for three consecutive months, followed by one injection every two months. (See **CLINICAL TRIALS** for dosing experience).

Special populations

Patients with hepatic and/or renal impairment

No specific studies in patients with hepatic and/or renal impairment were conducted with EYLEA. Available data do not suggest a need for a dose adjustment with EYLEA in these patients (see **Pharmacokinetic properties**).

Method of administration

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbiocide, have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended. RANZCO's guidelines for performing intravitreal therapy (August 2006) recommend the use of antimicrobial drops for 3-5 days following each injection.

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

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

Each pre-filled syringe or vial should only be used for the treatment of a single eye.

After injection any unused product must be discarded.

Instructions for use / handling

The pre-filled syringe and the vial are for single use only.

Prior to administration visually inspect the solution for injection. Do not use the vial or pre-filled syringe if particulates, cloudiness, or discolouration are visible.

Prior to usage, the EYLEA unopened vial or pre-filled syringe blister pack may be stored at room temperature (25°C) for up to 24 hours. After opening the vial or blister pack, proceed under aseptic conditions.

For the intravitreal injection a 30 G x ½ inch injection needle should be used.

Pre-filled syringe

1. When ready to administer EYLEA, open the carton and remove the sterilised blister pack. Carefully peel open the blister pack ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

2. Using aseptic technique, remove the syringe from the sterilised blister pack.

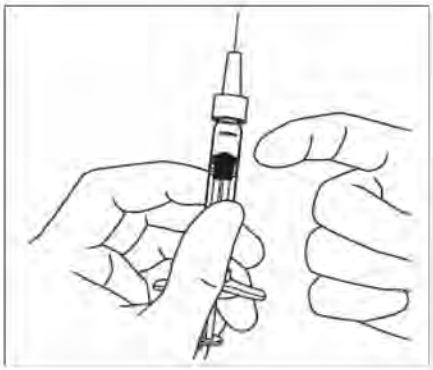
3. To remove the syringe cap, hold the syringe in one hand while using your other hand to grasp the syringe cap with the thumb and forefinger. Please note: Snap off (do not turn or twist) the syringe cap.

4. To avoid compromising the sterility of the product, do not pull back on the plunger.

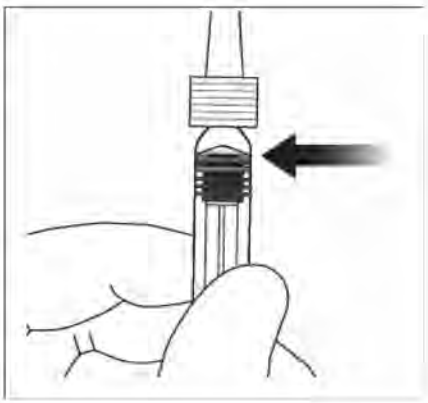
5. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

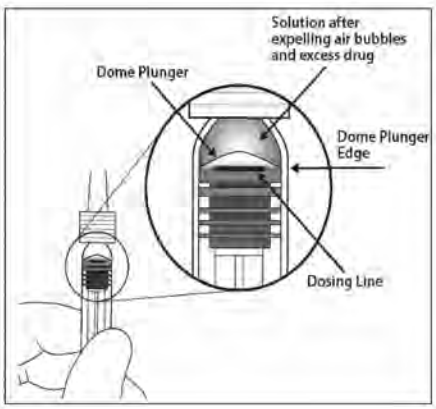
6. Remove the plastic needle shield.

7. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



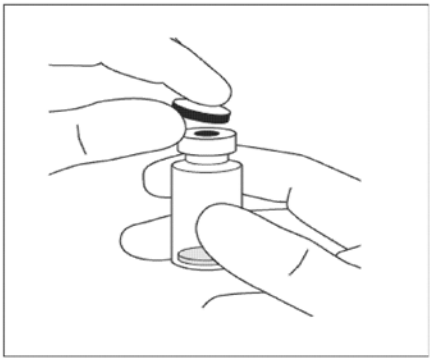
8. To eliminate all bubbles and to expel excess drug, slowly depress the plunger to align the cylindrical base of the dome tip with the black dosing line on the syringe (equivalent to 50 µL).



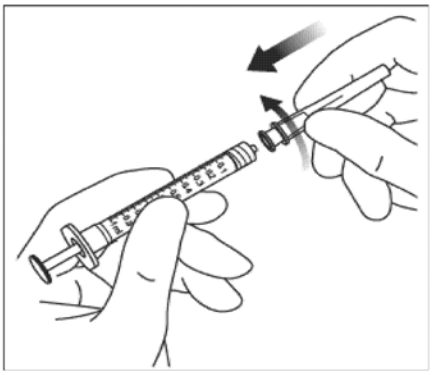


Vial

1. Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.

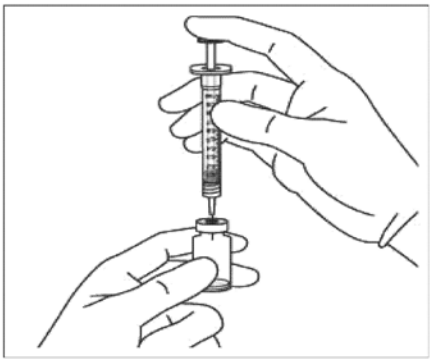


2. Attach the 18 G, 5-micron filter needle supplied in the carton to a 1 mL sterile, Luer-lock syringe.



3. Push the filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial.

4. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.

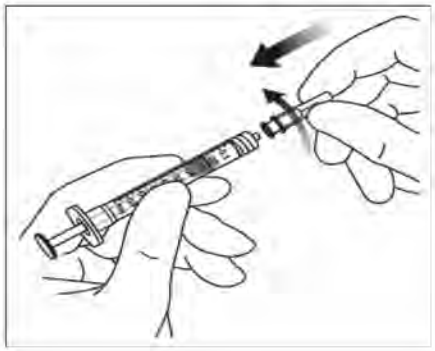


5. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in

order to completely empty the filter needle.

6. Remove the filter needle and properly dispose of it. Note: Filter needle is not to be used for intravitreal injection.

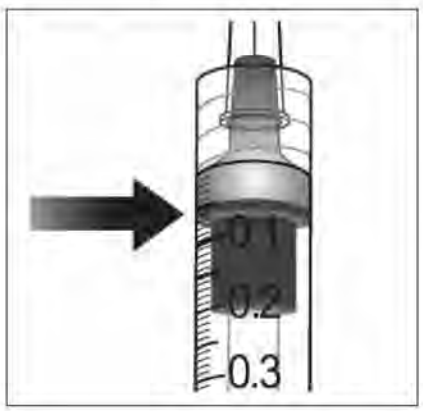
7. Using aseptic technique, firmly twist a 30 G x ½ inch injection needle to the Luer-lock syringe tip.

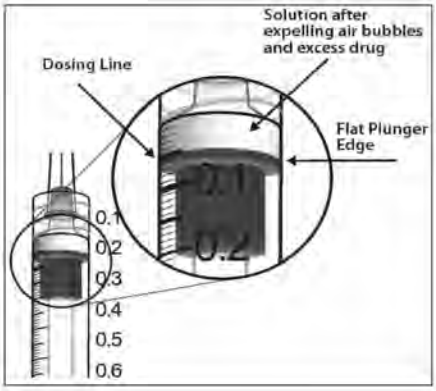


8. When ready to administer EYLEA, remove the plastic needle shield.

9. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.

10. Eliminate all bubbles and expel excess drug by slowly depressing the plunger so that the plunger tip aligns with the line that marks 0.05 mL (equivalent to 50 µL) on the syringe.





Incompatibilities

EYLEA must not be mixed with other medicinal products.

OVERDOSAGE

In clinical trials doses of up to 4 mg in monthly intervals and isolated cases of overdoses with 8 mg were generally well tolerated. Overdosing was associated with increased injection volume and subsequently with increased intraocular pressure. Therefore, in case of overdosage intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated. It is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

EYLEA is a sterile, clear, colourless to pale yellow, preservative-free, iso-osmotic aqueous 40 mg/mL solution for intravitreal injection.

EYLEA is supplied in a single-use vial or pre-filled syringe.

Each vial and pre-filled syringe provides a usable amount to deliver a single dose of 50 µL solution for intravitreal injection containing 2 mg aflibercept.

Pre-filled syringe

Each carton includes a sealed blister pack with a sterile pre-filled type I glass syringe, containing approximately 90 µL of extractable volume, sealed with an elastomeric

plunger stopper and an elastomeric tip cap that is part of a closure system with Luer lock adaptor. The syringe has a pre-attached plunger rod and a finger plate.

Vial

Each carton includes a type I glass vial containing approximately 100 µL of extractable volume, with an elastomeric rubber stopper, and an 18 G filter needle.

Shelf life and storage conditions

Shelf life: 12 months

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

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

Keep the vial in its carton in order to protect from light.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Limited
ABN 22 000 138 714
875 Pacific Highway
Pymble, NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE (S4)

DATE OF FIRST INCLUSION IN THE ARTG