Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Afibercept

Proprietary Product Name: Eylea

Sponsor: Bayer Australia Limited

July 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

I. Introduction to product submission

Submission Details

Type of Submission	New chemical entity
Decision:	Approved
Date of Decision:	17 February 2012
Active ingredient(s):	Aflibercept
Product Name(s):	Eylea
Sponsor's Name	Bayer Australia Limited 875 Pacific Highway Pymble NSW 2073
Dose form(s):	Solution for Intravitreal Injection
Strength(s):	40 mg/mL
Container(s):	Pre-filled syringe and vial
Pack size(s):	One unit per package
Approved Therapeutic use:	Eylea (aflibercept) is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).
Route(s) of administration:	Intravitreal
Dosage:	Injection volume is 50 µL of Eylea (equivalent to 2 mg aflibercept); one injection intravitreally monthly for three months followed by two monthly injections.
ARTG Number (s)	AUST R 180859 and AUST R 180860

Product background

Aflibercept (VEGF Trap-Eye, also abbreviated to VTE) is a new chemical entity, a biological substance that is a recombinant fusion glycoprotein consisting of sequences derived from human vascular endothelial growth factor (VEGF) receptor extracellular domains 1 and 2 are fused to the Fc portion of humanimmunoglobulin subtype G1 (IgG1). For more information on the structure of aflibercept, please refer to the separate quality findings below.

This AusPAR describes the application by Bayer Australia Ltd to register aflibercept (as Eylea) for

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

The proposed treatment regimen is intravitreal (IVT) injection of 50 µL solution (containing 2 mg aflibercept) once per month for three consecutive months, followed by one injection every two months.

Regulatory status

At the time of application, Eylea had also been submitted for registration in the European Union, Switzerland and the USA. These applications are all currently under evaluation with their

respective health authorities, with the exception of the USA, where the product was approved by FDA on the 18 November 2011.

Product information

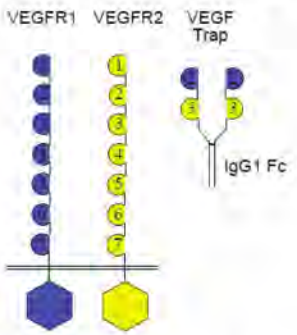
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Aflibercept is a recombinant protein consisting of sequences derived from human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of human IgG1. The extracellular domain sequences come from two different VEGF receptors, VEGFR1 (also known as Flt-1) and VEGFR2 (also known as KDR or Flk-1). Each of the VEGF receptors are composed of seven Ig domains in their extracellular regions, with Ig domains 2 and 3 contributing the majority of the binding energy for VEGF. Thus, the amino acid sequence of a single aflibercept subunit comprises Ig domain 2 from VEGFR1, fused to Ig domain 3 from VEGFR2, which is in turn fused to a Fc domain fragment of IgG1. There are no extraneous linker sequences between any of the peptide domains. The schematic structure of the drug substance is shown below:

Figure 1. Schematic structure



Aflibercept is a dimeric glycoprotein with a protein molecular weight of 96.9 kilo Daltons (kDa) ($C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$, 2 x 431 amino acids). It contains approximately 15% glycosylation to give a total molecular weight of 115 kDa. All five putative N-glycosylation sites on each polypeptide chain predicted by the primary sequence can be occupied with carbohydrate and exhibit some degree of chain heterogeneity, including heterogeneity in terminal sialic acid residues, except at the single unsialylated site associated with the Fc domain.

The disulfide bond structure of aflibercept determined by peptide mapping matches the known disulfide patterns of the VEGFR1 (Ig domain 2), VEGFR2 (Ig domain 3) and the IgG Fc domain. The C-terminus lacks the predicted lysine residue on the Fc moiety as expected.

Manufacture

The manufacturing of aflibercept drug substance involves growth of a suspension culture of Chinese Hamster Ovary cells (CHO K1) engineered to express aflibercept. The recombinant product is secreted into the culture medium and subsequently purified by chromatographic (Protein A affinity, cation exchange, anion exchange, hydrophobic interaction and size-exclusion chromatography), virus inactivation/filtration and membrane filtration techniques. Cell banking processes are satisfactory.

All viral/prion safety issues have been addressed, including use of animal-derived excipient supplements in the fermentation process and in cell banking.

Physical and chemical properties

Product related impurities include aggregates, truncated species, deamidated variants, charged variants and oxidised forms. The first four forms of impurity are controlled at drug substance release. It is well justified to exclude the testing of oxidised form at the drug substance release.

Specifications

Appropriate validation data were submitted in support of the test procedures.

Drug product

The drug product, 40 mg/mL, is formulated in 10 mM sodium phosphate buffer containing 40 mM NaCl, 0.03% (w/v) polysorbate 20 and 5% (w/v) sucrose, pH 6.2. Two presentations are available:

The vial presentation is supplied in a 2R ISO injection vial. The target fill volume for each vial is 278 µL (100 µL extractable volume) to ensure a single 50 µL injectable dose containing 2 mg aflibercept. One package includes one vial and one filter needle. The injection needle is not supplied.

The syringe presentation is supplied in glass 1 mL syringes. The target fill volume for each syringe is 165 µL (90 µL extractable volume). The syringe, when equipped with a 30 gauge, 0.5 inch needle, can deliver a single 50 µL injectable dose containing 2 mg aflibercept. One blister package contains one syringe. The injection needle is not supplied.

Manufacture

The drug product is sterilised by filtration.

Blisters containing the syringe are either hydrogen peroxide (H_2O_2)-sterilised or ethylene oxide (ETO)-sterilised.

Specifications

Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time/stressed conditions to characterise the stability profile of the product. Photostability data shows the product is not photostable and should be stored in its original package.

The real time stability data support a shelf life of "12 months when stored at 2°C to 8°C, protected from light", for both vial and syringe presentation.

Quality summary and conclusions

The draft PI, Consumer Medicine Information (CMI) and container/primary packaging labels are acceptable.

Summary of evaluation

The administrative, product usage, chemical, pharmaceutical and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

Batch release conditions of registration for clinical delegate

It is a condition of registration that the first five independent batches of Eylea are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

The sponsor should supply:

1. Certificates of Analysis of all active ingredient (drug substance) and final product.
2. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
3. Evidence of the maintenance of registered storage conditions during transport to Australia.
4. 3 vials or 3 syringes of each batch for testing by the Therapeutic Goods Administration OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency.

III. Nonclinical findings

Introduction

General comments

The overall quality of the nonclinical dossier was adequate. All pivotal safety-related studies were conducted under Good Laboratory Practice (GLP) conditions. A safety pharmacology study examining effects of aflibercept on cardiovascular parameters in rodents was non-GLP compliant; nevertheless, the study was well documented, and cardiovascular parameters were also examined as part of GLP compliant general repeat-dose toxicity studies in monkeys. Reports for several non-pivotal, non GLP repeat-dose toxicity studies in mice and rats were of poor quality in some respects; no group means were calculated, clinical signs and the histopathological findings were not tabulated, nor incidences per dose group calculated; the absence of group summary data (such that the results were not presented in a clear and concise

manner) is at odds with the TGA adopted EU guideline on repeated dose toxicity[1]. The pivotal toxicology studies were conducted with drug substance manufactured using the commercial process.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

Vascular endothelial growth factor (VEGF or VEGF-A) plays a critical role in angiogenesis. In age-related macular degeneration, VEGF promotes ocular neovascularisation and excessive vascular permeability and oedema. Aflibercept is designed to act as a soluble decoy receptor for VEGFR ligands.

Efficacy

In vitro, aflibercept was shown to bind to human VEGF-A with subpicomolar affinity (Kd for VEGF-A165, 0.497 pM; Kd for VEGF-A121, 0.360 pM). High affinity was also found for the related angiogenic molecule, PlGF-2 (placental growth factor 2; Kd value, 38.8 pM), which acts through VEGFR-1. Binding to aflibercept occurs with higher affinity than to the ligands' endogenous receptors (compared to respective Kd values for VEGF-A binding to VEGFR-1 and VEGFR-2, 10–30 pM and 75–760 pM[2] and ~170 pM for PlGF-2 binding to VEGFR-1[3]. The drug's ability to bind to PlGF may contribute to its pharmacological activity as PlGF is also implicated in the development of neovascular AMD[4]. Aflibercept also displayed affinity for PlGF-1 (placental growth factor 1; Kd value, 392 pM); in this case, though, affinity is below that for the endogenous receptor (170 pM for binding to VEGFR-13). The drug's affinity was similar for the animal and human VEGF isoforms among the species tested (mouse, rat, rabbit). Binding studies were not performed with monkey VEGF as its amino acid sequence is identical to human VEGF. In *in vitro* functional studies, aflibercept blocked VEGF-induced phosphorylation of VEGFR-2 and the resultant calcium mobilisation in human umbilical vein endothelial cells (HUVECs). *In vivo*, intravitreal (IVT) injection of aflibercept inhibited retinal neovascularisation in the mouse (oxygen-induced retinopathy model) and choroidal neovascularisation in the monkey (laser-induced), and normalised retinal vascular permeability in the rat (diabetic model).

Secondary pharmacodynamics and safety pharmacology

Aflibercept did not to bind to human VEGF-C or VEGF-D. In an immunohistochemical study examining potential cross-reactivity, no specific staining was found for aflibercept (≤25 µg/mL) against a panel of 33 normal human tissues. The Fc region of the aflibercept molecule did not mediate any complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro*.

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[1] CPMP/SWP/1042/99 Rev 1. Guideline on repeated dose toxicity. http://www.tga.gov.au/pdf/euguide/swp104209enrev1.pdf

[2] Robinson C.J. and Stringer S.E. (2001) The splice variants of vascular endothelial growth factor (VEGF) and their receptors. *J. Cell Sci.* 114: 853–865.

[3] Sawano A., Takahashi T., Yamaguchi S., Aonuma M. and Shibuya M. (1996) Flt-1 but not KDR/Flk-1 tyrosine kinase is a receptor for placenta growth factor, which is related to vascular endothelial growth factor. *Cell Growth Differ.* **7:** 213–221.

[4] Rakic J.M., Lambert V., Devy L., Luttun A., Carmeliet P., Claes C., Nguyen L., Foidart J.M., Noël A. and Munaut C. (2003) Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. *Invest. Ophthalmol. Vis. Sci.* 44: 3186–3193.

Specialised safety pharmacology studies were limited in scope. Instead, the sponsor has mostly relied on various general repeat-dose toxicity studies that incorporated relevant end points. This approach is acceptable under the applicable TGA adopted EU guideline[5]. Aflibercept had no effect on respiration in rats following IV administration (≤250 mg/kg over 30 min). There was no evidence of particular central nervous system (CNS) toxicity in the repeat-dose toxicity studies; lethargy in rats (at ≥2 mg/kg subcutaneously (SC) administered three times weekly) and reduced activity in monkeys (≥3 mg/kg intravenous (IV) once weekly) were observed, but occurred at doses beyond the maximum tolerated dose (MTD; based on body weight loss or substantial inhibition of body weight gain). Intravitreal (IVT) treatment produced no clinical signs in monkeys (≤4 mg/eye bilateral). Increases in blood pressure were observed in monkeys given aflibercept SC (15–30 mg/kg, twice weekly, but not IV (≤30 mg/kg once weekly). In a specialised study in mice and rats, SC administration of aflibercept increased systolic and diastolic blood pressure in both species that persisted until plasma concentrations of free aflibercept fell below 1 µg/mL. In addition to its function as a vascular growth factor, VEGF is involved in the regulation of blood pressure by modulating available nitric oxide and prostacyclin levels to promote vasodilatation[6]; these results therefore presumably reflect inhibition of circulating VEGF by aflibercept. No electrocardiogram (ECG) abnormalities were observed in monkeys treated with aflibercept SC or IV. Aflibercept did not affect thrombus formation or coagulation parameters in the rabbit (≤30 mg/kg IV). Wound healing was inhibited by aflibercept in rabbits at all doses tested (incisional and excisional models; reductions in blood vessel density, tensile strength, fibrous response and/or epidermal hyperplasia seen at ≥0.3 mg/kg IV); the finding is consistent with the known role of VEGF in wound repair (reviewed by Bao *et al.*, 2009[7]).

Pharmacokinetics

Free aflibercept, and sometimes also VEGF-bound aflibercept, were assayed in pharmacokinetic/toxicokinetic studies. The bound form is pharmacologically inactive.

Following IVT administration in monkeys, levels of free aflibercept in the vitreous were dose-proportional and declined with an estimated half-life of 40–64 h (independent of dose). Peak levels of free aflibercept in plasma were generally reached within 1–3 days post-dose and were detectable for up to 2 or 3 weeks. Bound aflibercept was detected in plasma with 24 h of dosing, peaking at 1–3 weeks post-dose; its apparent clearance was much slower compared to free aflibercept, remaining detectable in plasma in some animals for up to 18 weeks post-dose. Note, however, that the continuous formation of endogenous VEGF obfuscates the determination of the true half-life for bound aflibercept. The proportion of free:bound aflibercept increased with dose, consistent with saturable binding of endogenous VEGF. In rabbits given aflibercept IVT, half-lives for free aflibercept were determined to be 115 h in the vitreous and 157 h in plasma; peak plasma concentration (C_{max}) and overall exposure (area under the plasma concentration versus time response curve from time zero to infinity ($AUC_{0-\infty}$)) to free aflibercept in plasma was 950- and 310-times lower, respectively, compared to in the vitreous.

Greater than dose-proportional exposure was observed for free aflibercept in serum in rats and monkeys following SC administration. This may reflect that clearance comprises a saturable component, possibly related to VEGF binding. Again, long half-lives were observed for free

[5] CPMP/ICH/539/00. Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals, http://www.tga.gov.au/pdf/euguide/ich053900en.pdf

[6] He H., Venema V.J., Gu X., Venema R.C., Marrero M.B. and Caldwell R.B. (1999) Vascular endothelial growth factor signals endothelial cell production of nitric oxide and prostacyclin through flk-1/KDR activation of c-Src. *J. Biol. Chem.* 274: 25130–25135.

[7] Bao P., Kodra A., Tomic-Canic M., Golinko M.S., Ehrlich H.P. and Brem H. (2009). The role of vascular endothelial growth factor in wound healing. *J. Surg. Res.* 153: 347–358.

aflibercept in serum following IV and SC dosing (~40–50 h in the mouse and rat, and up to ~50–100 h in the monkey). Bioavailability by the SC route was high in mice (94%) and monkeys (85%) and moderate in rats (33%). No sex differences in pharmacokinetic profiles were observed for any route/species.

Distribution to the retina and choroid after IVT administration was shown in the rabbit, with peak and overall exposure to free aflibercept in these tissues ~5% of the corresponding values for the vitreous; half-lives were comparable for all three matrices (115–132 h). With IV dosing in mice, rats and monkeys, steady-state volumes of distribution were only slightly greater than the whole blood volume, consistent with limited distribution outside of the central compartment (as is typical for large molecular weight, protein-based drugs). Results from a tissue distribution study in rats with radioactively labelled (^{125}I)-aflibercept, administered IV, support this. Highest tissue concentrations of radioactivity were found in the liver, followed by other highly perfused tissues. The liver (and not the kidney) was identified as having the major role in the clearance of aflibercept. Consistent with this, functional nephrectomy did not significantly affect the serum kinetics of aflibercept in rats. Given aflibercept's protein nature, no classical biotransformation studies were conducted; this is in accordance with the relevant TGA adopted EU guideline[8].

Anti-aflibercept antibodies were formed in mice, rats and rabbits, and less commonly in monkeys. Their development was associated with decreased drug exposure in rabbits and the rodent species but rarely in monkeys. The aflibercept molecule contains multiple N-linked glycosylation sites. Differences in the extent of sialic acid occupancy were found to affect the drug's serum kinetics (in rats) but not its potency (assessed in *in vitro* binding and functional assays).

Pharmacokinetic drug interactions

No nonclinical studies were performed.

Toxicology

Acute toxicity

Single-dose toxicity studies, performed by the IV route in rats, revealed a low order of acute toxicity for aflibercept, with no deaths observed up to the highest dose tested (500 mg/kg).

Repeat-dose toxicity

Repeat-dose toxicity studies by the clinical route (IVT) were conducted in the cynomolgus monkey only (up to 8 months duration). To better characterise the systemic toxicological profile, SC studies were performed in mice (up to 8 weeks duration), rats (up to 13 weeks) and monkeys (up to 13 weeks), and IV studies were performed in the rabbit (2 weeks; in non pregnant animals as a pilot study for reproductive toxicity) and monkey (up to 6 months). Aflibercept is pharmacologically active in all of these species. IVT dosing was once per 4 weeks in the pivotal and most other studies (consistent with the initial phase of the clinical treatment regimen), or else once per 2 weeks or 6 weeks. The proposed clinical formulation was used in the pivotal IVT study; the strength of aflibercept varied with dose though, being the same as that for Eylea at the mid-dose level and double it at the high-dose level. SC and IV doses were administered more frequently than is proposed clinically for IVT administration, ranging from once per 2 weeks to up to 3 times weekly.

8 CPMP/ICH/302/95 Note for Guidance on Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals. http://www.tga.gov.au/pdf/euguide/ich030295en.pdf

Based on their short duration (≤3 months) and non-ocular route of administration, no rodent study sufficient to be regarded as pivotal has been provided with the current submission (this is not to say that they provided no useful information). A 6-month study in rodents was found not to be feasible due to the development of anti-aflibercept antibodies; repeated intravitreal administration is largely impractical in mice and rats. Considering this, the pre-eminence of the primate over the rodent as a relevant and feasible model for the assessment of the toxicity of the proposed product, and that there is existing experience with the pharmacological class, the reliance on the cynomolgus monkey as a single species for which there is a pivotal study is deemed to be acceptable. Group sizes were adequate; the small group size used in the monkey studies is typical but does limit their predictive value.

Relative exposure

Relative systemic exposure in selected toxicity studies has been calculated based on animal:human C_{max} and AUC for free aflibercept in plasma/serum (see Table 1 below). The human reference values used are from Clinical Study VGFT-OD-0702, obtained following IVT administration of 2 mg aflibercept (clinical formulation) to one eye of patients. The values have been doubled for the calculation here to reflect that Eylea may be administered to both eyes in clinical use.

Relative ocular exposure is considered based on dose adjusted for species differences in vitreous volume[9]; the IVT 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).

[9] Values for vitreous volumes of 3.2 mL in cynomolgus monkeys and 4.0 mL in humans have been used for the calculation here, in accordance with the approach to safety evaluation of Short (2008). Less conservative values (1.5 mL and 4.5 mL, respectively) were used by the author of the Nonclinical Expert Report.

Table 1. Relative exposure to free aflibercept in selected toxicity studies

Species	Study	Route; frequency	Dose	C_{max} (µg/mL)	$AUC_{0-28\,d}$ (µg·h/mL)	Exposure ratio#	
						C_{max}	AUC
Mouse (CD-1)	4 weeks PK01017[a]	SC; three times weekly	10 mg/kg	33.8	–	875	–
			15 mg/kg	82.2	–	2130	–
Rat (SD)	13 weeks VGFT-TX-02006[b]	SC; three times weekly	0.1 mg/kg	77.1	–	1995	–
			0.5 mg/kg	235	–	6090	–
			1 mg/kg	1701	–	44065	–
			2 mg/kg	915	–	23705	–
Monkey (Cynomolgus)	3 months VGFT-TX-02037[c]	SC; twice weekly	1.5 mg/kg	31.9	–	825	–
			5 mg/kg	109	–	2825	–
			15 mg/kg	286	–	7410	–
			30 mg/kg	721	–	18680	–
	3 months, juvenile VGFT-TX-05010[d]	IV; once weekly	0.5 mg/kg	9.54	1776	245	310
			3 mg/kg	73.8	19296	1910	3380
			30 mg/kg	830	163824	21505	28680
	6 months VGFT-TX-05009[e]	IV; once per 1–2/weeks	3 mg/kg	93.2	8832	2415	1545
			10 mg/kg	305	35952	7900	6295
			30 mg/kg	730	72336	18910	12665
	8 months VGFT-TX-05011[f]	IVT[2]; once/4 weeks	0.5 mg/eye	0.936	157.6	24	28
			2 mg/eye	6.97	1394	180	245
			4 mg/eye	16.9	3360	440	590
Human (AMD patients)	VGFT-OD-0702	IVT[1]	2 mg/eye	0.0193	2.856	–	–

= calculated as animal:human values, following doubling of the clinical reference values to reflect bilateral use; exposure ratios greater than 100 are rounded to the nearest 5; – = no data/not applicable;

[1] = unilateral administration; [2] = bilateral administration; data are the means of male and female values;

[a] = parameters obtained on day 22; [b] = parameters obtained on day 83; [c] = parameters obtained after dosing in week 13;

[d] = parameters obtained after dosing in week 13 (AUC_{0-168h} is multiplied by 4, accounting for dosing frequency)

[e] = parameters obtained after dosing in week 21; dosing was once per week to week 15, then once per 2 weeks;

(AUC_{0-168h} is multiplied by 2 to account for dosing frequency);

[f] = parameters obtained after the 7th dose.

Major findings

IVT administration of aflibercept was associated with an anterior segment/vitreous inflammatory response in monkeys. This was generally mild, usually peaked at 2 days post dose and was completely (anterior) or mostly (vitreous) reversed by 4 weeks post dose.

Administration of the vehicle alone also produced some inflammation. No angiographic or electro-retinographic changes were found in treated monkeys, nor were any ocular abnormalities observed in imaging and microscopic evaluations. Intraocular pressure was unaffected by the drug. Several-fold increases in intra ocular pressure (IOP) occurred immediately post dose, though, including following administration of the vehicle only, consistent with injection of a fluid bolus. No animal developed glaucomatous optic nerve head cupping in response to these IOP spikes. The only findings of toxicological significance in the IVT studies involved the nasal turbinates, with microscopic erosion and ulceration of the respiratory epithelium, often accompanied by chronic-active inflammation, seen at 2 and 4 mg/eye in the pivotal study. These lesions were generally mild and demonstrated to be reversible. Based on the absence of effects on other tissues, the nasal turbinate findings are considered more likely to result from local rather than systemic exposure (that is, by way of anastamotic connections between the ophthalmic and nasal venous plexuses or leakage into the nasal lacrimal duct). Cross-species exposure comparisons for such an effect are probably best made on a mg/kg basis: assuming 4 kg body weight for a monkey and 50 kg for a human (as a conservative measure), the lowest-observable-effect level (LOEL; 2 mg/eye) is more than 6 times the human dose and the no-observable-effect level (NOEL; 0.5 mg/eye) is >1.5 times the human dose. More pronounced effects on the nasal cavity were seen with systemic administration in monkeys, along with changes in numerous additional tissues, consistent with the very much higher exposure levels achieved. The nasal cavity findings included atrophy/loss of the septum and/or turbinates associated with necrotising inflammation. The other principal organs targeted were bone (such as osteocartilaginous exostoses of vertebrae; interference with growth plate maturation), kidney (increased glomerular mesangial matrix; glomerulopathy with tubular dilatation and cast formation), adrenals (decreased vacuolisation with eosinophilia of the cortex) and ovary (decreased number of maturating follicles, granulosa cells and/or theca cells). The vertebral changes were accompanied by myofibre atrophy of the overlying axial musculature along the vertebral arches or proliferation/degeneration of the microvasculature adjacent to the exostoses; kyphosis was observed in monkeys treated IV at ≥10 mg/kg/week for 13 weeks and at all dose levels (≥3 mg/kg every 1–2 weeks) in the 6-month study. Renal histopathological changes were associated with decreased serum albumin and/or total protein and increased blood urea nitrogen and urine protein levels. Vascular alterations in various tissues (proliferation/degeneration/fibrosis in duodenum, stomach, rectum, gallbladder, pancreas, heart and/or brain) and hepatic portal inflammation and periportal necrosis were also seen. No NOEL was established for systemic toxicity in the pivotal IV study in monkeys (<3 mg/kg every 1–2 weeks) but a NOEL was established in the IVT study (0.5 mg/eye/4 weeks for 8 months; relative exposure based on AUC was 28).

Mice and rats treated with aflibercept SC commonly and rapidly developed anti-aflibercept antibodies, leading to decreased drug exposure. The kidney was identified as the principal target organ for toxicity in the two rodent species, with glomerulonephritis routinely observed. This finding is consistent with deposition of circulating antigen-antibody complexes in the glomerulus. Other findings in treated mice and/or rats included vascular changes (haemorrhage, congestion and/or dilatation) in various tissues (kidney, liver, lungs and gastrointestinal tract), and changes in teeth (broken, thickened and altered colour) and bone (osteoporosis of femur).

Anti-aflibercept antibodies developed in monkeys at low frequency only in short term studies (4–13 weeks; SC, IV and IVT routes) but their development was more common in the 6 month IV study (39% of treated animals) and the 8 month IVT study (21% of treated animals). This was associated with toxicity in only one case; the sole animal that exhibited anti-aflibercept antibodies in a 13-week IVT study was the only one to show a severe ocular inflammatory response to treatment. Animals are poor models for immunogenicity in humans; the potential immunogenicity of the drug therefore requires particular clinical focus.

Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were included in the submission. Their omission is acceptable in accordance with the TGA adopted EU guideline[8] and justified on the basis that as a large protein the drug is not expected to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material, that chronic rodent studies are not feasible due to immunogenicity, that the drug does not have growth factor activity and did not display immunosuppressant activity in the general repeat-dose toxicity studies.

Reproductive toxicity

No specialised fertility study was conducted. Relevant data were obtained, though, as part of the 6 month IV general repeat-dose toxicity study in monkeys. In that study, females showed absent or irregular menses, associated with profound reductions in ovarian hormones (oestradiol, progesterone, and inhibin B) and increases in follicle stimulating hormone (FSH) levels, at all dose levels tested (≥3 mg/kg). Ovarian weight was reduced, accompanied by compromised luteal development and reduction of maturing follicles. Uterine and vaginal atrophy were also found. Following recovery, all aflibercept-treated females exhibited normal ovarian folliculogenesis and presence of medium to large sized corpora lutea; uterine and vaginal atrophy were also reversed. There were no aflibercept-related effects on male reproductive hormone levels (FSH, (luteinizing hormone) LH and testosterone). Decreased sperm motility and increased sperm abnormalities were evident at all doses; these effects were considered consequential upon fertility but were seen to be fully reversible after the treatment free phase. Due to adverse effects occurring at all the tested doses, No Observable Adverse Effect Levels (NOAELs) for effects on male and female fertility could not be established in the study (relative exposure at the lowest observable effect levels (LOELs) was 1545). Although more limited in terms of the parameters assessed, there were no findings to suggest impairment of fertility in the IVT studies in monkeys (relative exposure based on AUC in the pivotal study, ≤590).

Specialised reproductive toxicity studies conducted by the sponsor covered embryofetal development only. These were conducted in a single species (rabbit) and involved IV administration once every 3 days during the period of organogenesis. Placental transfer was demonstrated by the finding of free aflibercept in the amniotic fluid of pregnant rabbits. Abortions and increased post implantation loss were seen with dosing at 45 and 60 mg/kg. Maternotoxicity was evident at ≥15 mg/kg (as transient body weight loss). Treatment-related external and visceral fetal abnormalities, including malformations, were observed at all dose levels studied (≥3 mg/kg); skeletal malformations and variations were observed at 60 mg/kg and the incidence of incomplete ossification was increased at ≥3 mg/kg. Such effects are unsurprising given the critical role played by angiogenesis in fetal development. No NOEL was established for effects on embryofetal development. Plasma C_{max} and AUC values for free aflibercept at the lowest dose tested (3 mg/kg IV) were 56.1 µg/mL and 1935 µg·h/mL, respectively. These are 2907 times and 678 times higher than the C_{max} and AUC in patients after IVT administration of 2 mg aflibercept to one eye (Clinical Study VGFT-OD-0702).

No pre-/postnatal development study was conducted. Excretion of aflibercept in milk was not investigated in animals.

Pregnancy classification

The sponsor has proposed Pregnancy Category D. This categorisation was considered appropriate based on the drug's anti-angiogenic activity and the demonstration of teratogenicity in the rabbit. It matches the category for the related anti-VEGF IVT agent ranibizumab (Lucentis®).

Local tolerance

Local tolerance following IVT administration was evaluated in the general repeat-dose toxicity studies in monkeys. In a specialised study, no irritation or other local reactions attributable to aflibercept or the vehicle were found following IV, IM and SC administration in the rabbit; the study was adequately conducted. Compatibility with blood was demonstrated (human and monkey).

Paediatric use

Eylea is not proposed for use in children and adolescents. A repeat-dose toxicity study in juvenile monkeys (13 weeks duration; IV administration) revealed findings similar to those seen in mature animals, with the skeletal system a particular target of the drug. No study in juvenile animals by the IVT route has been conducted.

Nonclinical summary and conclusions

- The sponsor has conducted adequate nonclinical studies on the pharmacodynamics, pharmacokinetics and toxicity of aflibercept according to the relevant guidelines. All pivotal safety related studies were conducted according to GLP.
- Aflibercept acts 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. IVT injection of aflibercept was shown to inhibit retinal/choroidal neovascularisation in mouse and monkey models (oxygen- or laser-induced) and to normalise retinal vascular permeability in the rat (diabetic model).
- Secondary pharmacodynamic studies with aflibercept revealed high specificity. It did not bind to human VEGF-C or VEGF-D and did not exhibit cross-reactivity against a panel of human tissues. The Fc region of the molecule did not mediate complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity *in vitro*. Safety pharmacology examinations revealed increased blood pressure in rodents and monkeys and inhibition of wound healing in rabbits following systemic administration.
- Pharmacokinetic studies in rabbits and monkeys indicated a long half-life for free aflibercept (non-VEGF-bound) in the vitreous after IVT injection (115 h and 40–64 h in the respective species). Long half-lives were also evident in plasma. Distribution to the retina and choroid following IVT administration was shown in the rabbit. A major role was identified for the liver and not the kidney in the systemic clearance of aflibercept.
- Aflibercept displayed a low order of acute toxicity in rats by the IV route.
- Pivotal repeat-dose toxicity studies were conducted in the cynomolgus monkey only; chronic studies in rodents were not feasible due to the development of anti-aflibercept antibodies, which decreased drug exposure. The pivotal monkey studies involved IVT injection once every 4 weeks for 8 months and, to better characterise systemic toxicity, IV administration every 1–2 weeks for 6 months. IVT administration was associated with an anterior segment/vitreous inflammatory response in monkeys (as was the vehicle alone to a lesser degree; generally mild and completely or mostly reversed by 4 weeks post dose); among non-ocular tissues, the only treatment-related finding was erosion and ulceration of the respiratory epithelium of the nasal turbinates. Tissues identified as targets for toxicity in studies involving systemic administration (involving higher exposure) were bone, kidney, adrenals, ovary, and again the nasal cavity.
- Aflibercept was immunogenic in the laboratory animal species, though markedly less so in monkeys compared rodents or rabbits. In monkeys, this rarely affected pharmacokinetics and was associated with toxicity in only one case (finding of a severe ocular inflammatory response).

- No studies on genotoxicity or carcinogenicity were submitted.
- Effects consequent on male and female fertility were seen in monkeys treated with aflibercept IV (decreased sperm motility and increased abnormalities; irregular and absent menses associated with hormonal changes). In an embryofetal development study in rabbits, treatment with aflibercept (administered IV) produced abortions, increased post-implantation loss and caused fetal malformations (external, visceral and skeletal), variations and impairment of ossification.
- The nonclinical submission contained no major deficiencies. The scope of the nonclinical data set is consistent with EU guidelines for a protein-based drug.
- The nonclinical data provide reasonable, if limited evidence of efficacy.
- Increased blood pressure with aflibercept, identified following systemic administration in animals, is not considered likely to occur in patients with IVT treatment considering the lesser exposure.
- Ocular inflammation, seen in monkeys with IVT administration, being generally mild and reversible and partly attributable to the vehicle itself, is not considered to be a toxicologically significant finding in the context of therapy. Other findings in the repeat-dose toxicity studies are largely attributable to the drug's pharmacological action, disrupting the role of VEGF in microvascular maintenance. The nasal cavity is identified as the principal target for toxicity, with erosions and ulcerations of the epithelium occurring at exposure margins ≥6 in monkeys (based on mg/kg IVT doses; relative exposure at the NOEL, 1.5). [It is noted that the sponsor's Clinical Overview indicates that there was no evidence of such nasal effects in clinical trial participants.] Effects on the numerous other tissues that were seen in animals with repeated frequent systemic administration are not predicted to occur in patients treated with Eylea based on the existence of a large multiple of the maximum anticipated human exposure at the NOEL established in the monkey (that is, 28 times the clinical AUC).
- Given the limited predictivity of animals, assessment of the potential immunogenicity of aflibercept relies on clinical data.
- The absence of genotoxicity and carcinogenicity studies is acceptable; no particular concern for such effects is held.
- Teratogenicity was observed in the rabbit, beginning at a non maternotoxic dose. No NOEL was established for adverse effects on embryofetal development, the large exposure multiple at the LOEL notwithstanding. Considering these findings and given the pharmacological class (anti-angiogenic agent), placement in Pregnancy Category D is justified and the inclusion of appropriate precautionary statements in the Product Information document is warranted.
- There are no nonclinical objections to the registration of Eylea for the proposed indication.
- Amendments to the PI were also recommended.

IV. Clinical findings

Introduction

This application comprised a conventional clinical data set. All relevant individual patient data were supplied. There were 11 pharmacology/pharmacokinetic/dose finding studies. Two phase III pivotal studies were submitted. They were double blind, randomised, controlled two year

studies. The results submitted, however, were from the end of the first 12 months. There are long term studies that were only evaluable for safety information.

The studies contained in the submission appear to have been conducted according to good clinical practice (GCP).

Data from the following studies were provided:

Primarily pharmacokinetic and pharmacodynamic studies:

- Study VGFT-OD-0702.PK
- Study VGFT-OD-0307
- Study PDY6655
- Study PDY6656

Phase I studies:

- Study VGFT-OD-0502/14395 Part A (CLEAR-IT 1)
- Study VGFT-OD-0502/14395 Part C (CLEAR-IT 1)
- Study VGFT-OD-0603/14396 (CLEAR-IT 1b)
- Study VGFT-OD-0512/14805 (CLEAR-IT DME 1)
- Study VGFT-OD-0305
- Study VGFT-OD-0306

Phase II study:

- Study VGFT-OD-0508/14394 (CLEAR-IT AMD-2)

Pivotal efficacy studies:

- Study VGFT-OD-0605/14393 (VIEW 1)
- Study 311523 (VIEW 2)

Supportive studies:

- StudyVGFT-OD-0702/14262
- Study VGFT-OD-0706/13336 (DAVINCI)

Safety studies:

- Study VGFT-OD-0502/14395 Part B (CLEAR-IT 1)

Ongoing studies with limited safety data:

- Study VGFT-OD-0910/14832
- Study VGFT-OD-0819/14232 (COPERNICUS)
- Study 14130 (GALILEO)

Pharmacokinetics

Eylea is intended for intravitreal administration and systemic exposure is anticipated to be minimal. The sponsor provided pharmacokinetic studies following intravitreal administration and also following intravenous administration.

Systemic exposure following intravitreal administration

Study VGFT-OD-0702.PK/ 14263 was a pharmacokinetic sub-study to Study VGFT-OD-0702 (an open-label, long term Phase II safety and tolerability study in subjects with neovascular AMD receiving aflibercept 2 mg every 8 weeks). The study included six subjects with neovascular AMD but the demographic characteristics were not provided. VEGF-trap (aflibercept) was administered as a single 2 mg (50 µL) dose by intravitreal injection. Blood samples were collected at Times 0, 4 h, 8 h, 24 h, 48 h, 72 h, 96 h, 168 h, Day 15 and Day 29. VEGF-Trap concentrations were determined using an Enzyme-linked immunosorbent assay (ELISA) assay. The lower limit of quantification (LLOQ) of free VEGF Trap, VEGF Trap:VEGF complex and anti-VEGF Trap antibody were equal to 0.0156 mg/L, 0.0439 mg/L, and 0.238 mg/L respectively. Exposure to free VEGF-trap, expressed as the area under the plasma concentration time curve from time zero to the last measurable time point (AUC_{last}), was median (range) 0.0221 (0 to 0.474) mg.day/L. Exposure to VEGF-trap:VEGF complex expressed as AUC_{last}, was median (range) 4.67 (2.12 to 6.71) mg.day/L. The sponsor stated the exposure in terms of C_{max} to be approximately 5 fold lower than the maximum mean concentrations in studies of large IV doses (1 mg/kg IV - 4 mg/kg IV) but the reference the sponsor provided does not report AUC data[10] (Rudge 2007)[11]. Anti-VEGF Trap antibodies were unquantifiable in all subjects. Adverse events were not reported.

Study VGFT-OD-0603/14396 (CLEAR-IT 1b) was a double-masked, three arm (two randomised, one open-label) parallel group cohort study of the safety and tolerability of IVT-1 and IVT-2 formulations. VEGF-Trap was administered as a 4 mg intravitreal injection. Blood samples were collected for the measurement of VEGF-Trap concentrations. C_{max} was at 12 weeks. Mean (standard error (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-0512/14805 (CLEAR-IT DME 1) was an open label safety and tolerability study in five subjects with DME. The treatment was VEGF Trap-Eye, 4 mg as a single intravitreal injection of 100 µL volume. On Days 3 and 8, mean concentrations of VEGF Trap were 0.0502 and 0.0272 mg/L, respectively.

Intravenous pharmacokinetics

Study VGFT-OD-0305 was a double-masked, placebo controlled, sequential group, dose escalating, (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 5 mg/kg, 7 mg/kg, and 10 mg/kg) study of safety and bioeffect. The study included subjects with a diagnosis of visual impairment associated with neovascular AMD. Subjects were required to have visual loss due to subfoveal choroidal neovascularization (CNV) secondary to AMD, be 50 years of age or older, with no history of Type I or Type II diabetes, without significant cardiac, liver or kidney disease, or congestive heart failure (CHF); and without confounding ophthalmic issues.

The study treatments were:

1. VEGF Trap 0.3 mg/kg
2. VEGF Trap 1 mg/kg
3. VEGF Trap 3 mg/kg

[10] Rudge JS Proc Natl Acad Sci USA 2007:18363-18370

[11] Sponsor comment: Free VEGF Trap plasma concentrations following IVT administration of doses of up to 4 mg/eye (approximately 0.57 mg/kg, based on a 70 kg body weight) were approximately 2 to 3 orders of magnitude lower than free VEGF Trap plasma concentrations observed following IV administration of doses ≥ 1 mg/kg. Concentrations of bound VEGF Trap in plasma following IVT administration of doses of up to 4 mg/eye were approximately 20-fold lower than plasma bound VEGF Trap concentrations determined following IV administration of doses of 1 to 4 mg/kg.

4. Placebo

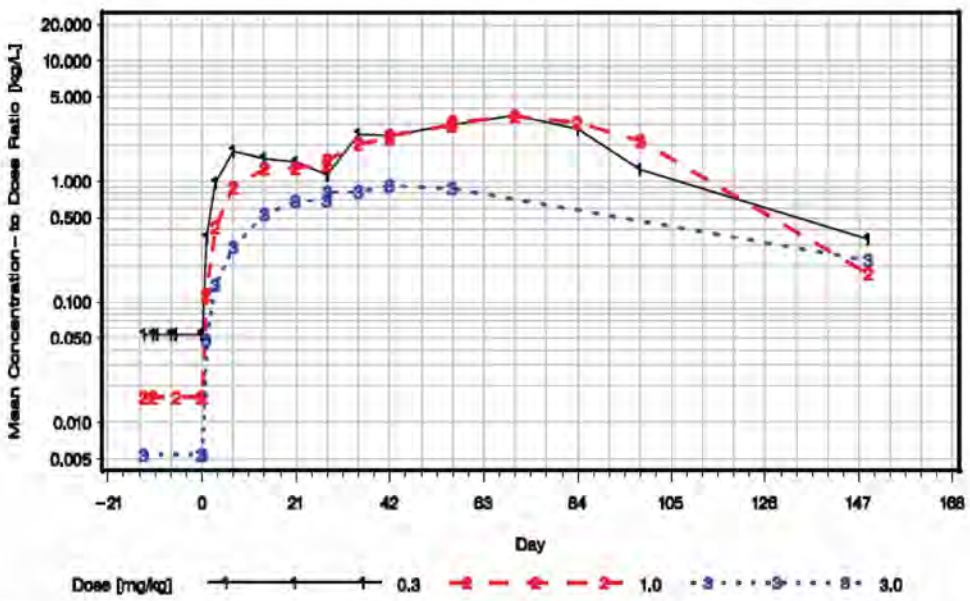
The treatments were delivered as an intravenous infusion over 1 hour. Subjects were to receive four doses over 8 weeks, followed by a 4 week observation period. The study was halted at the 3 mg/kg dose because of dose limiting toxicity.

The measures of biological effect were: visual acuity and optical coherence tomography (OCT). The outcome measures of safety were: adverse events (AEs), clinical laboratory tests, ophthalmic exam and anti-VEGF Trap antibodies. The PK measures were: plasma VEGF Trap levels.

A total of 26 subjects were included in the study: seven treated with VEGF Trap 0.3 mg/kg, seven treated with 1 mg/kg, six treated with 3 mg/kg, and none treated with 5 mg/kg, 7 mg/kg or 10 mg/kg. Twenty five subjects were included in the analysis: 14 (56%) females, 11 (44%) males, with an age range of 58 to 88 years.

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 (Figure 2). C_{max} for total VEGF reflected free VEGF levels and first dose trough concentrations and were 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.

Figure 2. Median Log-scaled Concentration of Adjusted VEGF Trap:VEGF Complex by Nominal Day.



Study VGFT-OD-0307 was a double masked, placebo controlled; sequential group, dose escalating, safety, tolerability and bioeffect study of VEGF Trap in patients with diabetic macular edema. The study was planned to include 24 subjects with escalating dose of VEGF Trap: 0.3 mg/kg, 1 mg/kg, or 3 mg/kg. However, due to the dose limiting toxicity observed in *Study VGFT-OD-0305*, only the 0.3 mg/kg dose level was examined. There were four intravenous infusions at 2 week intervals. The study included subjects ≥ 25 years of age, with a hemoglobin A1c between 9 and 10% and on a stable regimen of anti-diabetic medication; with nonproliferative or mild proliferative diabetic retinopathy; retinal edema; ≥ 2 prior focal, grid or panretinal photocoagulation treatments for which scars did not involve the center of the macula ≥ 12 weeks prior to Day 1; a best corrected visual acuity of 20/40 or worse according Early

Treatment Diabetic Retinopathy Study (ETDRS); and retinal thickness ≥ 250 µm in the macular region as measured by OCT. The study included nine subjects: six treated with 0.3 mg/kg, three treated with placebo. There were five females, four males, and the age range was 57 to 81 years. At the 0.3 mg/kg dose intravenously, mean (standard deviation (SD)) C_{max} was 600 (202) ng/mL for free VEGF Trap, 1522 (659) ng/mL for VEGF Trap:VEGF and 1590 (699) ng/mL for total VEGF Trap.

Study PDY6655 was a Phase I, single centre, randomised, single dose, crossover, pharmacokinetic (PK) study in healthy volunteers to compare the pharmacokinetics and pharmacodynamic (PD) of intravenous and subcutaneous administration of aflibercept. The study included 40 healthy male subjects aged 18 to 45 years. The study treatments were: aflibercept 2.0 mg/kg as an intravenous infusion over 1 hour, and as a subcutaneous injection. The aflibercept was presented as 4 mL of 25 mg/mL solution. The treatments were administered as single doses followed by 6 week observation period. The treatment periods were separated by 1 to 2 weeks. The PK outcome measures were: C_{max}, AUC, apparent volume of distribution at steady state (Vss), clearance and half life (t½). The PD outcome measures were: systolic blood pressure, diastolic blood pressure, heart rate, mean arterial pressure, plasma renin activity, angiotensin I, aldosterone, and free endogenous VEGF. The safety outcome measures were: AEs, clinical laboratory test, injection site reactions, and anti-aflibercept antibodies.

AUC and C_{max} were slightly higher for Period 2, indicating some carry over. For Period 1, for free aflibercept mean (co-variance (CV%)) AUC was 177 (33) µg•day/mL and peak plasma concentration (C_{max}) was 44.4 (36) µg/mL for intravenous and AUC was 84.9 (30) µg•day/mL and C_{max} was 7.76 (39) µg/mL for subcutaneous (Table 2). For Period 1, for bound aflibercept mean (CV%) AUC was 57.7 (19) µg•day/mL and C_{max} was 1.84 (22) µg/mL for intravenous and AUC was 47.3 (27) µg•day/mL and C_{max} was 1.60 (27) µg/mL for subcutaneous (Table 3). The mean (90% CI) ratio for AUC, subcutaneous/ intravenous, was 0.51 (0.46 to 0.56).

Table 2. Mean (CV%) free aflibercept pharmacokinetic parameters

Route of administration	Period	T_{max}* (day)	C_{max} (µg/mL)	AUC (µg.day/mL)	$T_{1/2,z}$ (day)	Vss (L)	CL (L/day)
i.v.	1	0.04 (0.04–0.17)	44.4 (36)	177 (33)	4.75 (10)	5.74 (29)	0.938 (27)
	2	0.04 (0.04–2)	45.3 (31)	181 (32)	4.91 (11)	5.69 (28)	0.891 (26)
s.c.	1	2 (1.08 – 4)	7.76 (39)	84.9 (30)	4.80 (15)	-	-
	2	2 (0.083–4)	9.29 (32)	98.4 (32)	4.88 (8)	-	-
ratio s.c./ i.v.			0.207 (46)	0.549 (37)			

*: median (range)

Table 3. Mean (CV%) bound aflibercept pharmacokinetic parameters

Route of administration	Period (n)	T_{max}* (day)	C_{max} (µg/mL)	T_{last} (day)*	C_{last} (µg/mL)	AUC(0-t) (µg.day/mL)
i.v.	1 (20)	28 (14 – 28)	1.84 (22)	42 (42 – 42)	1.27 (31)	57.7 (19)
	2 (18)	21 (14 – 28)	2.26 (27)	42 (42 – 42)	1.44 (35)	76.4 (26)
s.c.	1 (20)	28 (14 - 28)	1.60 (27)	42 (28 - 42)	1.10 (44)	47.3 (27)
	2 (20)	28 (7 – 28)	2.05 (30)	42 (42 – 42)	1.27 (46)	69.5 (29)

*: median (range)

Study PDY6656 was a single centre, Phase I, randomised, double blind, placebo controlled, sequential ascending dose study of intravenous aflibercept. The study included healthy male subjects 18 to 45 years of age; non-smoker; 18≤ body mass index (BMI) ≤28 kg/m^2; with normal vital signs and no symptomatic hypotension. The study treatments were aflibercept 1 mg/kg, 2 mg/kg and 4 mg/kg, and placebo. There were three cohorts of 16 subjects: twelve treated with aflibercept and four treated with placebo. The treatments were administered as a single dose by intravenous infusion over 1 hour. The pharmacodynamic outcome measures were: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), plasma active renin, aldosterone and angiotensin I; markers of endothelium dysfunction (plasma endothelin-1, E-selectin, cyclic guanosine 3'5' monophosphate (cGMP), and urine nitrites/nitrates); renal function; and VEGF. The safety outcome measures were: AEs and laboratory tests. The study included 48 subjects: 12 treated with 1 mg/kg, 12 with 2 mg/kg, 12 with 4 mg/kg and 12 with placebo. The age range was 21 to 45 years. For free aflibercept mean (CV%) C_{max} was 18.2 (18) µg/mL for the 1 mg/kg dose, 39.7 (27) µg/mL for the 2 mg/kg dose and 78.6 (15) µg/mL for the 4 mg/kg dose; and mean (CV%) AUC was 64.8 (20) µg.day/mL for the 1 mg/kg dose, 180 (20) for the 2 mg/kg dose and 419 (21) for the 4 mg/kg dose. Bound aflibercept concentrations were not dose dependent and the proportion of bound aflibercept decreased with increasing dose. However, C_{max} and AUC for total aflibercept were dose proportional (Table 4).

Table 4. Mean (CV%) total (free + bound) aflibercept pharmacokinetic parameters.

Dose (mg/kg)	C_{max} (µg/mL)	$AUC_{(0-t)}$ (µg.day/mL)	AUC (µg.day/mL)	$T_{½\lambda z}$ (day)
1	18.2 (18)	100 (16)	120 (16)	19.4 (20)
2	39.7 (27)	253 (17)	297 (17)	18.1 (10)
4	78.6 (15)	494 (18)	543 (17)	13.6 (26)

Evaluator's overall conclusions on pharmacokinetics

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 median AUC_{last} was (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 a 4 mg intravitreal injection, for the aflibercept: VEGF complex the time to peak plasma concentration (T_{max}) was 12 weeks and the C_{max} was (mean (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, the 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 aflibercept 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, the mean AUC (CV%) and C_{max} for free aflibercept were 177 (33) µg.day/mL and 44.4 (36) µg/mL, respectively, for intravenous administration. For a 2.0 mg subcutaneous administration, the mean AUC was 84.9 (30) µg.day/mL and the C_{max} was 7.76 (39) µg/mL. For bound aflibercept, the mean (CV%) AUC was 57.7 (19) µg.day/mL and the mean C_{max} was 1.84 (22) µg/mL following intravenous administration. The AUC and C_{max} were 47.3 (27) µg.day/mL and 1.60 (27) µg/mL, respectively, for bound aflibercept following 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) µg. day/mL for a 2 mg/kg dose and 419 (21) µg. day/mL for a 4 mg/kg dose (Study PDY6656). Bound aflibercept concentrations were not dose proportional whereas the C_{max} and AUC for total aflibercept were dose proportional.

Pharmacodynamics

Pharmacodynamic data were provided for the systemic effects of aflibercept.

In *Study PDY6655* there was an increase in SBP that was maximal at Day 16: the mean increase was 5.54 mmHg for subcutaneous administration and 6.50 mmHg for intravenous administration (Figure 3). There was an increase in DBP that was maximal at Day 16: mean

increase of 6.32 mmHg for subcutaneous administration and 7.22 mmHg for intravenous administration (Figure 4). For both routes of administration there was an increase in MAP, which was maximal at Day 16 at around 6 mmHg (Figure 5). Plasma renin activity and aldosterone concentrations decreased (Figures 6 and 7) whereas angiotension I had little change. Free VEGF concentrations were decreased within 1 day of administration and appeared to have recovered by Day 29 (Figure 8).

Figure 3. Summary plots of 24-hour mean SBP (mean ± SE, mm Hg).Change from baseline

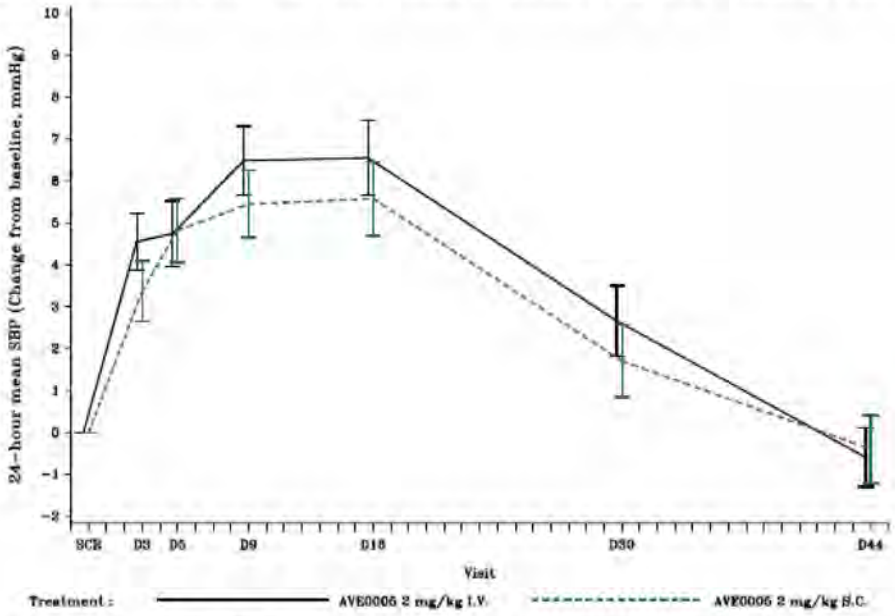


Figure 4. Summary plots of 24 hour mean DBP (mean ± SE, mm Hg); change from baseline

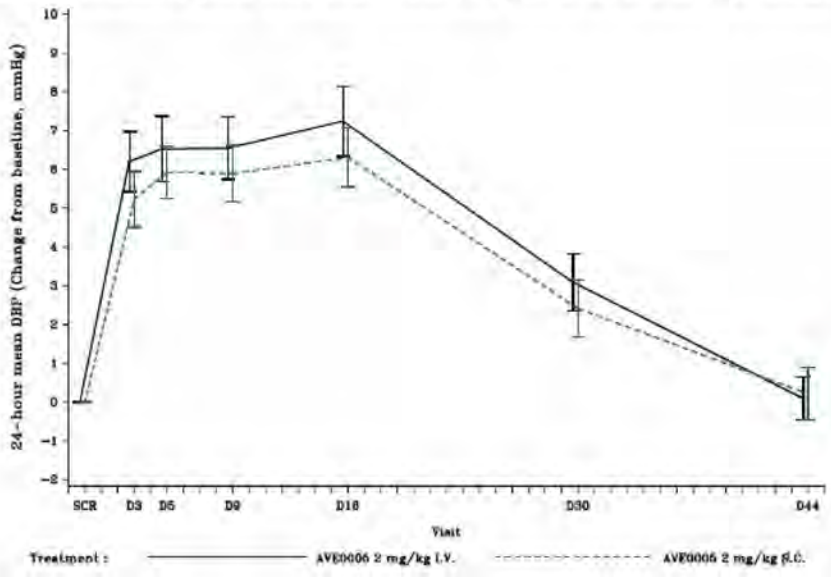
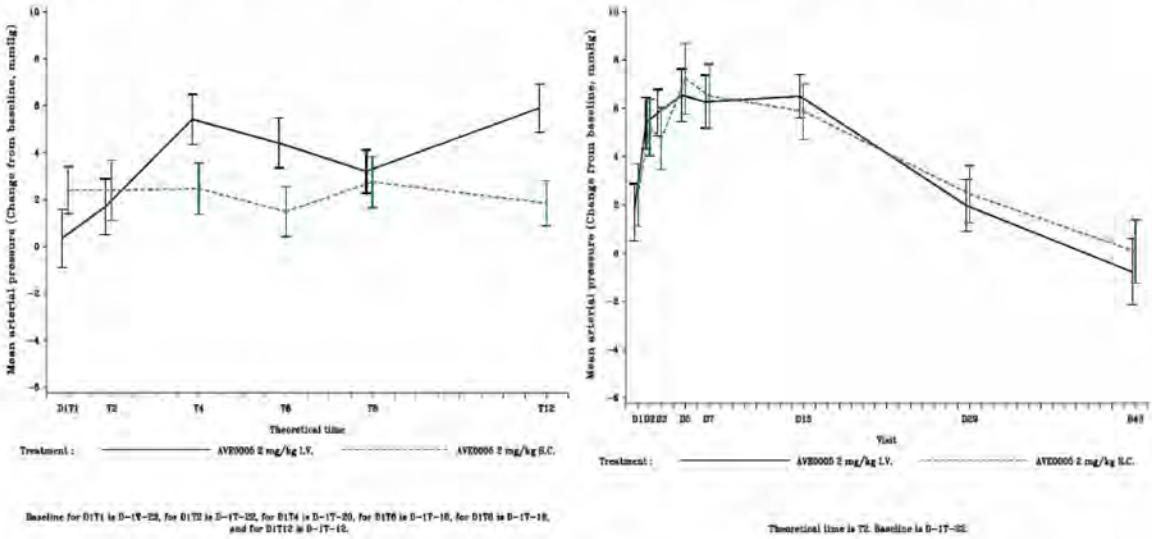


Figure 5. Summary plots of mean arterial blood pressure (mean ± SEM, mm Hg) – Day 1 profile (left panel) and Day 1 to Day 43 profile (right panel); change from baseline



Baseline for D1T1 is D-1T-02, for D1T2 is D-1T-02, for D1T4 is D-1T-20, for D1T6 is D-1T-16, for D1T8 is D-1T-16, and for D1T12 is D-1T-12.

Theoretical time is T2. Baseline is D-1T-02.

Figure 6. Summary plots of plasma active renin concentrations (mean ± SEM, pg/mL) – Change from baseline

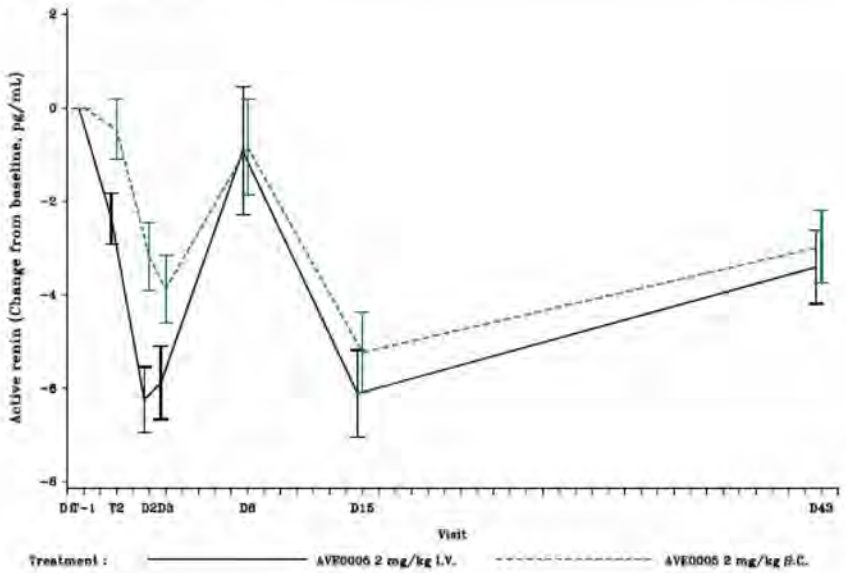


Figure 7. Summary plots of plasma aldosterone concentrations (mean ± SEM, pmol/L) – Change from baseline

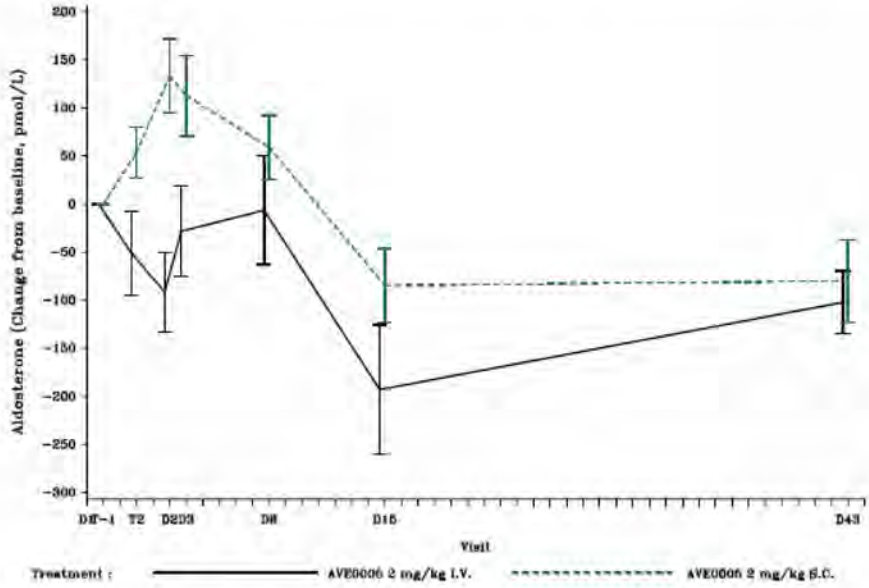
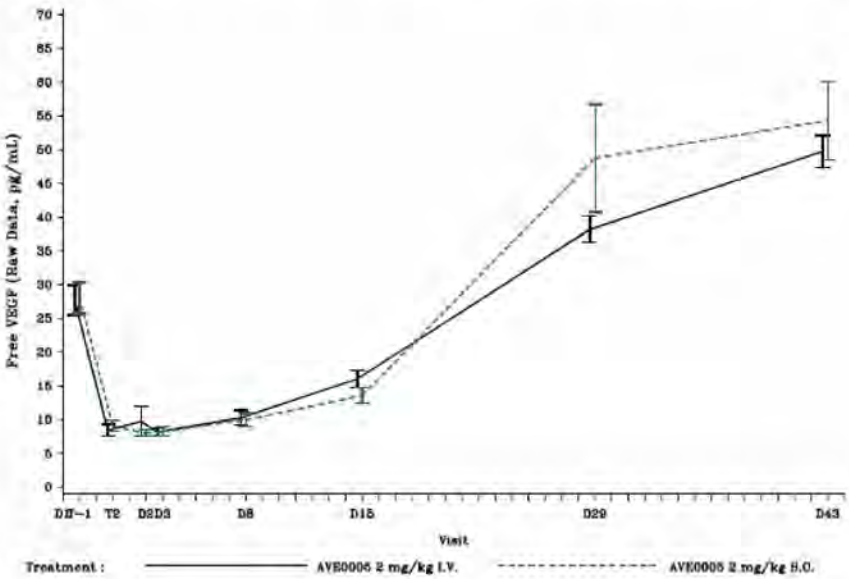


Figure 8. Summary plots of plasma free VEGF concentrations (mean ± SE, pg/mL). Raw data



In *Study PDY6656*, SBP, DBP and MAP increased in the active treatment groups. In comparison with placebo, the mean (95% CI) maximum increase in SBP was 5.16 (0.74 to 9.58) mmHg for 1 mg/kg, 4.90 (0.58 to 9.22) mmHg for 2 mg/kg and 10.27 (5.77 to 14.78) mmHg for 4 mg/kg. In comparison with placebo, the mean (95% CI) maximum increase in DBP was 5.31 (2.36 to 8.26) mmHg for 1 mg/kg, 5.13 (2.19 to 8.06) mmHg for 2 mg/kg and 10.67 (7.68 to 13.66) mmHg for 4 mg/kg. In comparison with placebo, the mean (95% CI) maximum increase in MAP was 3.12 (-

0.13 to 6.37) mmHg for 1 mg/kg, 4.41 (1.15 to 7.66) mmHg for 2 mg/kg and 10.67 (7.68 to 13.66) mmHg for 4 mg/kg. A significant increase in SBP was noted for 16 days at the 1 mg/kg and 2 mg/kg dose levels and for 44 days at the 4 mg/kg dose level. There was a decrease in heart rate that reached statistical significance in the 4 mg/kg group. In comparison with placebo, the mean (95% CI) maximum decrease in heart rate was 1.17 (-2.42 to 4.76) beats per minute (bpm) for 1 mg/kg, 3.26 (-0.32 to 6.85) bpm for 2 mg/kg and 4.48 (0.90 to 8.06) bpm for 4 mg/kg.

Plasma rennin activity and aldosterone concentrations were reduced with all three dose levels of aflibercept. There was no significant change in angiotensin I concentrations. There was no consistent change in plasma endothelin concentrations, plasma E-selectin concentrations, plasma cyclic guanosine 3′,5′-monophosphate (cGMP) or urinary nitrate excretion. There was no change in proteinuria or microalbuminuria. Plasma free VEGF increased in all three active treatment groups from 2 weeks after treatment.

Evaluator's overall conclusions on pharmacodynamics

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.

Efficacy

Introduction

The sponsor provided data from a development program for aflibercept for the indication of AMD. The efficacy data were provided by 11 studies (see Introduction above).

Phase I and dose finding studies

Study VGFT-OD-0502/14395 Part A

Study VGFT-OD-0502/14395 Part A (CLEAR-IT 1) was a Phase I, open label, dose escalation safety and tolerability study. The study included:

- Males and females ≥50 years of age
- With subfoveal CNV secondary to AMD
- central retinal/lesion thickness (CR/LT) ≥ 250 µm as measured by OCT
- Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA of 20/40 (73 letters) or worse
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography
- If history of prior ocular or major systemic surgery, including fine needle biopsy/aspiration, placement of a central venous access device or removal/biopsy of a skin lesion, procedures performed at least 12 weeks prior to Visit 2 (Day 1)
- Normal ECG

- Treated or untreated blood pressure ≤140/90 mmHg or isolated systolic pressure of ≤160 mmHg with diastolic pressure of ≤85 mmHg

The study treatments were VEGF Trap-Eye at dose levels:

1. 0.05 mg,
2. 0.15 mg,
3. 0.50 mg,
4. 1 mg,
5. 2 mg and
6. 4 mg.

There was sequential enrolment and dose escalation. The treatments were administered as single doses by intravitreous injection. This was followed by an open-label extension phase of aflibercept 4 mg by intravitreous injection on an as required basis.

The efficacy outcome measures were:

- CR/LT as determined by OCT; total lesion size,
- CNV size, and
- Classic CNV size by fluorescein angiography and best corrected visual acuity (BCVA).

The safety outcome measures were:

- AEs,
- Laboratory tests,
- Ophthalmic investigations, and
- Antibodies to VEGF-trap.
- PK assessments were also performed.

The study enrolled 21 subjects: three subjects were treated with 0.05 mg, three with 0.15 mg, three with 0.50 mg, six with 1 mg, three with 2 mg, and three with 4 mg. Nine subjects continued into the open-label study. All subjects were included in the analysis. There were 13 (61.9%) females, eight (38.1%) males and the age range was 62 to 85 years. The dose groups were similar in baseline CR/LT and visual acuity.

The greatest effect was in the 2 mg to 4.0 mg dose grouping. At Day 57, the mean (SD) percentage change in CR/LT was -2.0 (20.9) in the 0.05 mg to 0.5 mg grouping, -21.1 (25.9) in the 1.0 mg group and -33.8 (23.0) in the 2.0 mg to 4.0 mg grouping, p=0.0074 (Table 5). Change from baseline in total macular volume was greatest in the 4 mg dose group but macular volume was greatest in this group at baseline and result could represent regression to the mean (Table 6). Change in visual acuity was greatest in the 2.0 mg to 4.0 mg dose grouping (Table 7). The mean (SD) change from baseline at Day 57 was 1.6 (5.0) in the 0.05 mg to 0.5 mg group; -0.2 (14.39) in the 1.0 mg group; and 15.0 (16.84) in the 2.0 mg and 4.0 mg group; but this difference did not reach statistical significance, p=0.1057. There was no significant change from baseline, or between treatment groups, in fluorescein angiography.

Table 5. Percentage change in CR/LT from Baseline (LOCF)

Day/Pooled Group	N	Mean % Change	Standard Deviation	Median % Change	Range of % Changes	P Value (1-Sample t-Test)
Day 29						
A (0.05 to 0.5 mg)	8[a]	-1.4	18.4	2.5	-26 to 28	
B (1.0 mg)	6	-27.9	19.3	-25.4	-57 to -5	
C (2.0 and 4.0 mg)	6	-33.8	22.2	-23.2	-68 to -16	
Total	20	-19.1	24.0	-18.4	-68 to 28	0.0021
Day 43						
A (0.05 to 0.5 mg)	8	-3.2	23.5	-13.8	-24 to 39	
B (1.0 mg)	6	-24.5	27.6	-25.8	-57 to 17	
C (2.0 and 4.0 mg)	6	-26.4	33.4	-27.9	-66 to 21	
Total	20	-16.5	28.7	-14.5	-66 to 39	0.0185
Day 57						
A (0.05 to 0.5 mg)	8	-2.0	20.9	0.1	-28 to 39	
B (1.0 mg)	6	-21.2	25.9	-26.8	-47 to 19	
C (2.0 and 4.0 mg)	6	-33.8	23.0	-26.4	-69 to -10	
Total	20	-17.3	25.8	-14.8	-69 to 39	0.0074

Note: The larger the percentage decrease from baseline, the more favorable the effect on retinal thickness.

[a] Baseline CR/LT was not determined for 2 patients in the 0.05 mg cohort. The screening value was used as the baseline value for 1 of the 2 patients. For the other patient, no screening value was available.

Table 6. Summary of Total Macular Volume (mm^3) by OCT (Full Analysis Set) Study Part A

		VGFT Dose Regimen						
		0.05mg (N=3)	0.15mg (N=3)	0.50mg (N=3)	1.00mg (N=6)	2.00mg (N=3)	4.00mg (N=3)	Total (N=21)
Baseline	n	1	2	2	6	3	3	17
	Mean	9.7	6.9	7.4	9.0	7.4	10.3	8.6
	SD		0.64	0.76	2.16	0.92	3.95	2.26
	Median	9.7	6.9	7.4	8.1	7.5	9.4	7.6
	Min,Max	10,10	6,7	7,8	7,12	6,8	7,15	6,15
Value	n	3	3	3	6	3	3	21
	Mean	9.6	6.7	6.7	8.1	6.7	7.2	7.6
	SD	0.84	0.30	0.47	1.44	0.27	1.34	1.36
	Median	9.6	6.7	6.9	7.9	6.7	6.6	6.9
	Min,Max	9,10	6,7	6,7	6,10	6,7	6,9	6,10
Change from Baseline	n	1	2	2	6	3	3	17
	Mean	-0.9	-0.2	-0.7	-1.0	-0.7	-3.1	-1.2
	SD		0.23	1.39	2.00	0.66	4.58	2.23
	Median	-0.9	-0.2	-0.7	-0.7	-0.8	-0.7	-0.7
	Min,Max	-1,-1	-0,-0	-2,0	-4,2	-1,0	-8,-0	-8,2
	1 sample t-test p-value							0.0431
Change ANCOVA p-values	Overall							0.5084

Table 7. Change in Visual Acuity from Baseline (LOCF).

Day/Pooled Group	N	Mean Change	Standard Deviation	Median Change	Range of Changes	P Value (1-Sample t-Test)
Day 29						
A (0.05 to 0.5 mg)	9	1.1	3.02	2.0	-5 to 4	
B (1.0 mg)	6	-0.7	10.39	0.5	-20 to 10	
C (2.0 and 4.0 mg)	6	14.3	15.15	11.0	0 to 35	
Total	21	4.4	11.41	2.0	-20 to 35	0.0937
Day 43						
A (0.05 to 0.5 mg)	9	0.6	5.43	0.0	-11 to 6	
B (1.0 mg)	6	1.2	11.02	4.0	-20 to 10	
C (2.0 and 4.0 mg)	6	13.5	15.73	12.5	-3 to 31	
Total	21	4.4	11.78	1.0	-20 to 31	0.1002
Day 57						
A (0.05 to 0.5 mg)	9	1.6	5.00	2.0	-8 to 10	
B (1.0 mg)	6	-0.2	14.39	4.0	-29 to 11	
C (2.0 and 4.0 mg)	6	15.0	16.84	15.5	-7 to 35	
Total	21	4.9	13.27	4.0	-29 to 35	0.1057

Study VGFT-OD-0502/14395 Part C

Study VGFT-OD-0502/14395 Part C (CLEAR-IT 1) was a randomised double masked Phase I study of safety and tolerability. The inclusion criteria were similar to Study VGFT-OD-0502/14395 Part A with the variations of:

- 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 neovascularization) as assessed by fluorescein angiography (FA)

The study treatments were:

1. 1. VEGF Trap-Eye 0.15 mg
2. 2. VEGF Trap-Eye 4 mg

The treatments were administered as a single dose of 100 µL volume by intravitreal injection. During the open label phase the dose was 4 mg on a as needed (pro re nata; PRN) basis for up to 12 months.

The efficacy outcome measures were:

- CR/LT as determined by OCT;
- Total lesion size; CNV size,
- Classic CNV size by FA; and
- BCVA.

The safety outcome measures were:

- AEs,
- Clinical laboratory tests,
- Ophthalmic examinations of both the study eye and the fellow eye, and
- Antibodies to VEGF Trap-Eye.

The study included 28 subjects: 14 were treated with 0.15 mg; and 14 were treated with 4 mg. There were 15 (53.6%) males, 13 (46.4%) females and the age range was 55 to 89 years. Twenty two subjects entered the open label extension. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline CR/LT and visual acuity.

Improvement in CR/LT from baseline was greatest at Day 29 and there was significantly greater improvement in the 4.0 mg group: mean % change (SD) was -13.3 (20.55) for the 0.15 mg dose and -34.2 (17.08) for the 4.0 mg dose, p<0.0001 (Table 8). There was a significant decrease in total macular volume (TMV) at Day 43 that was greater in the 4.0 mg group: mean (SD) change from baseline -0.8 (1.21) for the 0.15 mg dose and -1.0 (0.86) for the 4.0 mg, p=0.0295. There was greater improvement in visual acuity in the 4.0 mg group at Day 43: mean (SD) 0.7 (6.93) for 0.15 mg and 8.9 (12.28) for 4.0 mg, p=0.0237. There was no significant change in FA.

Table 8. Percentage Change in CR/LT from Baseline (LOCF)

Day/Group	N	Mean % Change	Standard Deviation	Median % Change	Range of % Changes	P Value (1-Sample t-Test)
Day 29						
0.15 mg	14	-13.3	20.55	-7.3	-57 to 13	
4.0 mg	14	-34.2	17.08	-37.4	-57 to 0	
Total	28	-23.8	21.39	-25.5	-57 to 13	<0.0001
Day 43						
0.15 mg	14	-5.9	19.96	-1.4	-53 to 23	
4.0 mg	14	-23.8	22.31	-28.1	-53 to 28	
Total	28	-14.8	22.68	-9.1	-53 to 28	0.0018
Day 57						
0.15 mg	14	-11.3	22.09	-6.6	-57 to 35	
4.0 mg	14	-25.2	25.89	-35.5	-55 to 19	
Total	28	-18.3	24.65	-18.9	-57 to 35	0.0005

Note: The larger the percentage decrease from baseline, the more favorable the effect on retinal thickness.

Study VGFT-OD-0603/14396

Study VGFT-OD-0603/14396 (CLEAR-IT 1b) was a double-masked, three arm (two randomised, one open-label) parallel group cohort study of the safety and tolerability of IVT-1 and IVT-2 formulations. The study included adults at least 50 years of age; male or female; with a diagnosis of AMD due to active primary or recurrent subfoveal choroidal neovascularization (CNV); with BCVA in the range of 20/40 to 20/400 (corresponding to a letters-read score of 73 to 20 when using the ETDRS visual acuity charts) in the study eye. One eye was designated as the study eye, the other as the fellow (untreated) eye.

The study treatments were VEGF Trap-Eye 4 mg single injections from Day 1 to Week 12:

1. 4 mg in 100 µL q4w IVT-1 formulation
2. 4 mg in 100 µL q4w IVT-2 formulation
3. 4 mg in 50 µL q4w open label cohort (IVT-2)

After Week 12 the subjects could enter an open label follow-on phase with treatments of 4 mg of the same formulation used in the primary analysis phase PRN for up to 12 months. All the treatments were administered by intravitreal injection.

The efficacy outcome measures were:

- Change from baseline in BCVA as measured by ETDRS letter score
- Patients who gain at least 15 letters of vision from baseline
- Change in CNV area from baseline

- Change from baseline in CRT as measured by OCT
- Patients showing complete resolution of FA leakage
- Change from baseline in total lesion area and area of fluorescein leakage as assessed by FA

The safety outcome measures were:

- Ophthalmic examination (including IOP),
- Laboratory tests,
- Treatment emergent adverse events (TEAEs) and
- Anti-VEGF Trap antibodies.

No sample size calculations were performed and no hypothesis tests were undertaken.

The study included 20 subjects: six randomised to IVT-1, six randomised IVT-2; and eight treated with open label IVT-2. Two subjects withdrew from the 12 week primary analysis phase, one withdrew after the first dose and the second died 47 days following the last dose. Seventeen subjects entered the open label phase. There were 16 (80%) females, four (20%) males and the age range was 63 to 87 years. The treatment groups were similar in demographic characteristics. Apart from greater mean retinal thickness in the IVT-2 randomised group, the treatment groups were similar in baseline disease characteristics.

Hypothesis tests were not performed on the efficacy outcome measures. There was a similar change in central retinal thickness for the two formulations: mean (SD) change from baseline to Week 12: -188.8 (123.52) for IVT-1 and -288.6 (148.97) for IVT-2. The mean (SD) change in visual acuity to Week 12 was 4.7 (5.24) for IVT-1 and 9.6 (18.61) for IVT-2. There were no apparent differences between the groups in FA.

Study VGFT-OD-0512/14805(CLEAR-IT DME 1)

This was an open label safety and tolerability study in five subjects with diabetic macular oedema (DME). The study included: males and non-pregnant, non-lactating females, age ≥18 years with DME; best corrected ETDRS visual acuity score of ≥ 24 letters (20/320 or better) and ≤ 73 letters (20/40 or worse); on clinical examination, definite retinal thickening due to DME involving the center of the macula; retinal thickness at the center point ≥ 250 microns.

The treatment was VEGF Trap-Eye, 4 mg as a single intravitreal injection of 100 µL volume. The efficacy outcome measures were:

- ERT and total macular volume as determined by OCT;
- Best-corrected ETDRS visual acuity; and
- Area of vascular leak on FA.

The Safety outcome measures were:

- AEs,
- Clinical laboratory tests,
- Ophthalmic examinations, and
- Antibodies to VEGF Trap.

The PK measure was plasma concentration of VEGF Trap.

The study included five subjects, all received treatment, one withdrew from the active observation phase and another subject withdrew from long-term follow-up. There were three (60%) females, two (40%) males and the age range was 56 to 75 years.

The study protocol did not intend any hypothesis testing on efficacy measures. On Day 43 the median (range) % change from baseline in ERL was -37.5 (-100 to -15.9) %, and the median (range) % change from baseline in TMV was -12.36 (-24.36 to -1.6) %. At Day 29 the median (range) change in visual acuity was 9 (-1 to 10) letters. There was no consistent pattern of change in FA.

Study VGFT-OD-0305

In *Study VGFT-OD-0305* hypothesis tests were not reported on the efficacy outcome measures. The greatest improvement in visual acuity appeared to be in the VEGF Trap 3.0 mg/kg intravenous group at Day 29: 11.0 letters. The 0.3 mg/kg and 1.0 mg/kg groups appeared to be similar to placebo. The greatest decrease in ERT was also in the 3.0 mg/kg group at Day 29: -153.7 μm. The greatest improvement in macular volume was also in the 3.0 mg/kg group at Day 29: -1.75 mm^3. There were no changes in FA.

Study VGFT-OD-0306

Study VGFT-OD-0306 was an open label, long term safety and tolerability extension study of intravenous VEGF Trap in subjects with neovascular AMD who had been included in Study VEGF-OD-0305. The study treatments were VEGF Trap at the same dose level the subjects had been treated with in Study VEGF-OD-0305: either 0.3 mg/kg or 1 mg/kg, by intravenous administration every 2 weeks. Placebo patients from Study VGFT-OD-0305 were assigned to VEGF Trap at the dose level at which they were enrolled in Study VGFT-OD-0305. The efficacy outcome measures were:

- Visual acuity (ETDRS),
- Retinal thickness (OCT) and
- Funduscopic examination,
- Fundus photography, and
- FA.

The safety outcome measures were:

- AEs,
- Clinical laboratory tests, and
- Ophthalmic exam.

Treatment duration was for up to 106 days. There were seven subjects: four subjects treated with 0.3 mg/kg, 3 subjects treated with 1 mg/kg. There were five females, two males and the age range was 68 to 84 years. Six of the seven subjects had a slight reduction in ERT in the study eye and six of seven subjects had slight reductions in macular volume in the study eye.

Phase II Studies of Treatment Regimens

Study VGFT-OD-0508/14394 (CLEAR-IT AMD-2) was a multicentre, double blind, randomised, parallel group, efficacy and safety study. The study compared five dosing regimens for aflibercept.

The inclusion criteria included:

- Males and non-pregnant, non-lactating females ≥50 years of age
- Subfoveal CNV secondary to AMD
- Central retinal (including lesion) thickness ≥300 μm as measured by OCT
- ETDRS BCVA of 73 letters to 34 letters

- For previously treated patients with minimally classic or occult lesions, a loss of ≥5 ETDRS letters (or ≥1 Snellen line) in BCVA over the 6 months prior to the start of the study
- Lesion greatest linear diameter (GLD) ≤5400 μm (including blood, scars, atrophy and neovascularisation) as assessed by FA
- Subretinal haemorrhage making up ≤50% of total lesion size and sparing the fovea
- Area of scar ≤25% of total lesion
- Sufficiently clear ocular media, including the lens, to allow photography of the retina
- Treated or untreated blood pressure ≤150/90 mmHg or isolated systolic pressure of ≤160 mmHg with diastolic pressure of ≤85 mmHg

The fellow eye inclusion criteria included:

- Subfoveal CNV secondary to AMD
- Clear ocular media and clear lens(es) to permit good quality stereoscopic fundus photography
- BCVA 20/40 (73 letters) or worse

The dosing regimens were:

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

The treatments were administered by intravitreal injection, in an injection volume of 100 μL.

The primary efficacy outcome measure was retinal thickness determined by OCT at Week 12. The secondary efficacy outcome measures were:

- BCVA determined by ETDRS
- Fundus photography and FA
- Vision related quality of life

Hypothesis tests were performed using analysis of covariance (ANCOVA). A sample size calculation was not performed.

The safety outcome measures were:

- IOP,
- Ophthalmic examinations,
- Physical examination,
- ECG,
- AEs and
- Clinical laboratory tests.

Plasma concentrations of aflibercept were measured in order to estimate PK parameters.

A total of 159 subjects were enrolled and 157 of these received treatment: 32 in the 0.5 mg every 4 weeks (q4w) group, 32 in the 0.5 mg every 12 weeks (q12w), 31 in the 2 mg q4w, 31 in the 2 mg q12w and 31 in the 4 mg q12w. A total of 153 subjects completed to Week 12. There

were 98 (62.4%) females, 59 (37.6%) males and the age range was 53 to 94 years. The treatment groups were mismatched in gender but similar in other baseline demographic variables.

At Week 12 the greatest reduction in CRT was in the 2 mg q4w group: mean (SD) change -169.2 (138.46) µm; followed by the 0.5 mg q12h group: -153.5 (113.3) µm and the 4 mg q12h group: -139.8 (228.59) µm (Table 9). However, at all other time points over the 52 weeks the 4 mg q12w group had the greatest reduction in central retinal thickness. The greatest improvement in visual acuity through to Week 52 was in the 2 mg q4w group. The greatest improvement in vision related quality of life through to Week 52 was in the 4 mg q12w group. The greatest decrease in total lesion size by FA was in the 2 mg q4w group at Week 52, followed by the 4 mg q12w group.

Table 9. Mean Change from Baseline in Central Retinal/Lesion Thickness through Week 52* by Treatment Group (Full Analysis Set)

	0.5mg q4	0.5mg q12	2mg q4	2mg q12	4mg q12	Total
Week 1						
n	31	32	31	31	28	153
Mean change (µm)	-89.3	-107.7	-96.1	-69.5	-157.6	-103.0
SD (µm)	100.74	85.22	102.02	94.47	160.41	112.70
p-value						< 0.0001
Week 12						
n	32	32	31	31	31	157
Mean change (µm)	-153.5	-75.6	-169.2	-56.3	-139.8	-118.8
SD (µm)	113.30	110.64	138.46	133.05	228.59	155.31
p-value						< 0.0001
Week 16						
n	32	32	31	31	31	157
Mean change (µm)	-163.3	-139.6	-182.7	-107.4	-208.6	-160.2
SD (µm)	108.13	126.41	146.75	112.22	202.07	145.34
p-value						< 0.0001
Week 52						
n	32	32	31	31	31	157
Mean change (µm)	-125.0	-108.5	-143.0	-111.6	-161.4	-129.7
SD (µm)	117.54	106.56	156.15	135.80	215.68	150.27
p-value						< 0.0001

Note: The larger the decrease from baseline, the more favorable the effect on retinal thickness
* Missing values were imputed by LOCF
** P-value based on 1-Sample t-Test

Pivotal efficacy studies

Study VGFT-OD-0605/14393

Methods

This was a multicentre, double masked, randomised, active controlled, parallel group, non-inferiority efficacy and safety study. The submission included the report of the first 52 weeks of the study (total intended duration of 2 years). The study was conducted in the US and Canada.

The inclusion criteria included:

- Men and women ≥50 years of age
- Active primary subfoveal choroidal neovascularization (CNV) lesions secondary to AMD including juxtafoveal lesions that affected the fovea as evidenced by FA in the study eye

- CNV must be at least 50% of total lesion size.
- ETDRS BCVA of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
- The exclusion criteria included:
- Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins
- Prior treatment with anti-VEGF agents in the study eye (prior, but not concurrent, treatment with anti-VEGF therapy in the fellow eye was allowed)
- Total lesion size >12 disc areas (DAs) (30.5 mm^2, including blood, scars and neovascularisation) as assessed by FA in the study eye
- Subretinal hemorrhage that was either 50% or more of the total lesion area, or if the blood was under the fovea and was one or more DAs in size in the study eye
- Scar or fibrosis, making up >50% of total lesion in the study eye
- Scar, fibrosis, or atrophy involving the center of the fovea
- Presence of retinal pigment epithelium (RPE) tears or rips involving the macula in the study eye
- History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye
- Presence of other causes of CNV, including pathologic myopia (spherical equivalent of 8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye
- History or clinical evidence of diabetic retinopathy, diabetic macular edema (DME) or any other vascular disease affecting the retina, other than AMD, in either eye
- Prior vitrectomy in the study eye
- History of retinal detachment or treatment or surgery for retinal detachment in the study eye
- Any history of macular hole of Stage 2 and above in the study eye
- Any intraocular or periocular surgery within 3 months of Day 1 on the study eye
- Prior trabeculectomy or other filtration surgery in the study eye.
- Uncontrolled glaucoma (defined as IOP ≥25 mmHg despite treatment with anti-glaucoma medication) in the study eye
- Active intraocular inflammation in either eye
- Active ocular or periocular infection in either eye
- Any ocular or periocular infection within the last 2 weeks prior to screening in either eye
- Any history of uveitis in either eye
- Active scleritis or episcleritis in either eye
- Presence or history of scleromalacia in either eye
- Aphakia or pseudophakia with absence of posterior capsule in the study eye
- Previous therapeutic radiation in the region of the study eye
- History of corneal transplant or corneal dystrophy in the study eye

- Significant media opacities, including cataract, in the study eye which might interfere with VA, assessment of safety, or fundus photography (FP)
- Any concurrent intraocular condition in the study eye (such as cataract) that, in the opinion of the investigator, could have required either medical or surgical intervention during the 96 week study period.
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might have affected interpretation of the results of the study or rendered the subject at high risk for treatment complications.
- The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to Day 1.
- Females who were pregnant, breastfeeding or of childbearing potential, unwilling to practice adequate contraception throughout the study.

The study treatments were:

1. 1. Aflibercept 2 mg q4w
2. 2. Aflibercept 0.5 mg q4w
3. 3. Aflibercept 2 mg every 8 weeks (q8w)
4. 4. Ranibizumab 0.5 mg q4w

Subjects were randomised in balanced groups by Interactive Voice Response System (IVRS). Treatments were performed by an unmasked investigator but efficacy and safety evaluations were performed by a masked investigator. Blinding of subjects was maintained in the q8w group through "sham" injections (performed without a needle, active drug or ocular penetration). Treatments were administered by intravitreal injections. In each subject one eye was treated and the other not treated (fellow eye). The allocation of the treated eye was not by randomisation.

The primary efficacy outcome measure was the proportion of subjects who maintained vision at Week 52. Maintenance of vision was defined as a loss of fewer than 15 letters in ETDRS letter score compared to baseline. The secondary efficacy outcome measures were:

- 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
- Change in CNV area from baseline to Week 52

Additional efficacy outcome measures were:

- Change from baseline in BCVA at Week 12
- Change from baseline in CRT at Week 52
- Proportion of subjects who lost 15 or more letters of vision ("moderate" vision loss) at Week 52
- Proportion of subjects who gained 30 or more letters of vision at Week 52
- Proportion of subjects who lost 30 or more letters of vision ("severe" vision loss) at Week 52
- Change from baseline in scores for National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) subscales (near activities, distance activities, vision dependency) at Week 52

- Change from baseline in total lesion area as assessed by FA at Week 52
- Proportion of subjects with VA of 20/40 or better at Week 52
- Proportion of subjects with VA of 20/200 or worse at Week 52
- Proportion of subjects who gained ≥0 letter of vision at Week 52
- Proportion of subjects who gained ≥10 letters of vision at Week 52
- Change from baseline in classic CNV area at Week 52
- Proportion of subjects showing complete resolution of FA leakage at Week 52
- Change from baseline in area of fluorescein leakage as assessed by FA at Week 52

The safety outcome measures were

- AEs,
- Vital signs,
- IOP,
- Clinical laboratory tests and
- Anti-aflibercept antibodies.

The schedule of study visits up to Week 52 was presented in the report.

Statistical Issues

The study was designed as a non-inferiority study with the condition for non-inferiority being that the 95% CI for the difference in the proportion of subjects who maintained vision at Week 52 compared to baseline (ranibizumab – aflibercept) was entirely below 10%. 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
3. aflibercept 2 mg q8w versus ranibizumab

The sample size calculation assumed that 90% of subjects treated with 0.5 mg ranibizumab would maintain vision and that 90% of subjects treated with aflibercept would also maintain vision, defined the non-inferiority margin at 10% and determined that in order to achieve a power of 90% at an α of 0.05, then 191 subjects per group would be required. Assuming a dropout rate of approximately 30%, enrollment of 300 subjects per group would be necessary.

Results

A total of 2063 subjects were screened and of these, 1217 subjects were randomised: 304 were treated with aflibercept 2 mg q4w, 304 with 0.5 mg q4w, 303 with 2 mg q8w, and 306 with ranibizumab 0.5 mg q4w. A total of 103 (8.5%) subjects discontinued prematurely, 18 (1.5%) due to AE, and 13 (1.1%) subjects died. There were 711 (58.8%) females, 499 (41.2%) males, with an age range of 49 to 99 years: 86 (7.1%) aged <65 years, 255 (21.1%) ≥65 to <75 years and 869 (71.8%) ≥75 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline disease severity, prior medical history and concomitant medication.

The primary efficacy outcome was similar for all four treatment groups and non-inferiority was demonstrated for all three aflibercept dosing regimens compared with ranibizumab. 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. Non-inferiority was also demonstrated in the

full analysis group and in sensitivity analyses (Table 10). The proportion maintaining vision at Week 52 in the full analysis group was: 289 (95.1%) for aflibercept 2 mg q4w, 286 (95.0%) for 0.5 mg q4w, 284 (94.4%) for 2 mg q8w and 285 (93.8%) for ranibizumab. There was no significant difference between the treatment groups in the secondary efficacy outcome measures but the results were supportive of non-inferiority. The mean change from baseline in CNV area was–4.6 (5.47) for aflibercept 2 mg q4w, –3.5 (5.27) for 0.5 mg q4w, –3.4 (6.02) for 2 mg q8w and –4.2 (5.59) for ranibizumab.

Table 10. Sensitivity Analyses of the Proportion of Subjects who Maintained Vision at Week 52 (Full Analysis Set).

	Ranibizumab	VEGF Trap-Eye		
	0.5Q4 (N = 304)	2Q4 (N = 304)	0.5Q4 (N = 301)	2Q8 (N = 301)
Last observation carried forward				
Subjects who maintained vision at Week 52 (%)	285 (93.8%)	289 (95.1%)	286 (95.0%)	284 (94.4%)
Difference (%) (95.1% CI)		-1.3 (-5.0 2.4)	-1.3 (-4.9, 2.4)	-0.6 (-4.4, 3.2)
Observed Values*				
Subjects who maintained vision at Week 52 (%)	259/273 (94.9%)	271/285 (95.1%)	254/263 (96.6%)	256/266 (96.2%)
Difference (%) (95.1% CI)		-0.2 (-3.9, 3.4)	-1.7 (-5.1, 1.7)	-1.4 (-4.9, 2.1)
Worst observation carried forward				
Subjects who maintained vision at Week 52 (%)	284 (93.4%)	289 (95.1%)	286 (95.0%)	281 (93.4%)
Difference (%) (95.1% CI)		-1.6 (-5.4, 2.1)	-1.6 (-5.3, 2.1)	0.1 (-3.9, 4)
All drop-outs counted as non-responders				
Subjects who maintained vision at Week 52 (%)	267 (87.8%)	279 (91.8%)	267 (88.7%)	265 (88.0%)
Difference (%) (95.1% CI)		-3.9 (-8.8, 0.9)	-0.9 (-6, 4.3)	0.1 (-5.1, 5.3)
All treatment failures counted as non-responders				
Subjects who maintained vision at Week 52 (%)	280 (92.1%)	287 (94.4%)	278 (92.4%)	279 (92.7%)
Difference (%) (95.1% CI)		-2.3 (-6.3, 1.7)	-0.3 (-4.5, 4)	-0.6 (-4.8, 3.7)

Note: Maintenance of vision was defined as a loss of < 15 letters in the ETDRS letter score
Difference is ranibizumab minus VEGF Trap-Eye; CI was calculated using a normal approximation.
*Observed values are presented by visit in Post-text Table 14.2.1/18

There was no significant difference between the groups in:

- Change from baseline in BCVA at Week 12
- Proportion of subjects who lost 15 or more letters of vision ("moderate" vision loss) at Week 52
- Proportion of subjects who gained 30 or more letters of vision at Week 52
- Proportion of subjects who lost 30 or more letters of vision ("severe" vision loss) at Week 52
- Proportion of subjects who gained ≥ 0 letter of vision at Week 52
- Proportion of subjects who gained 10 or more letters of vision at Week 52
- Proportion of subjects with VA of 20/40 or better at Week 52
- Proportion of subjects with VA of 20/200 or worse at Week 52

- Change from baseline in total lesion area as assessed by FA at Week 52
- Change from baseline in CRT at Week 52
- Change from baseline in scores for NEI VFQ-25 subscales (near activities, distance activities, vision dependency) at Week 52
- Change from baseline in classic CNV area at Week 52
- Change from baseline in area of fluorescein leakage as assessed by FA at Week 52.

However, 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: 159 (52.8%) subjects compared with 193 (63.5%); difference (95% CI) -10.7 (-18.5 to -2.8) %, p=0.0084.

Study 311523

Methods

Study 311523 (VIEW 2) was a multicentre, double masked, randomised, active controlled, parallel group, non-inferiority efficacy and safety study. The study was almost identical in design to *Study VGFT-OD-0605/14393 (VIEW 1).* The submission contained the report of the first 52 weeks of the study. The study was conducted at 186 centres in 26 countries.

The inclusion criteria, exclusion criteria and study treatments were identical to *Study VGFT-OD-0605/14393 (VIEW 1).*

The efficacy outcome measures were the same, except for the additional outcome measure: change in scores of the EQ-5D questionnaire from screening at Week 52.

Statistical Issues

The sample size determination was the same as for *Study VGFT-OD-0605/14393 (VIEW 1)* except for the additional requirement to recruit a planned target population to be enrolled in Japan of 140 subjects with a minimum of 120 subjects, based on regional regulatory requirements.

Results

A total of 2031 subjects were screened and 1240 subjects were randomised: 313 to aflibercept 2 mg q4w, 311 to 0.5 mg q4w, 313 to 2 mg q8w and 303 to ranibizumab 0.5 mg q4w. At least one dose of study medication was received by 1204 subjects. A total of 125 (10.1%) subjects discontinued prematurely: 25 (2.0%) due to AE, and nine (0.7%) died. There were 667 (55.5%) females and 535 (44.5%) males, 185 (15.5%) subjects were aged <65 years, 385 (32.0%)≥65 to <75 years and 731 (71.8%) ≥75 years. The age range was 50 to 93 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline disease characteristics, past medical history and concomitant medication.

The primary efficacy outcome was similar for all four treatment groups and non-inferiority was demonstrated for all three aflibercept dosing regimens compared with ranibizumab. 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. Non-inferiority was also demonstrated in the full analysis group and in sensitivity analyses (Table 11). The proportion maintaining vision at Week 52 in the full analysis group was: 292 (94.5%) for aflibercept 2 mg q4w, 282 (95.27%) for 0.5 mg q4w, 292 (95.42%) for 2 mg q8w and 276 (94.85%) for ranibizumab. There was no significant difference between the treatment groups in the secondary efficacy outcome measures but the results were supportive of non-inferiority.

Table 11. Sensitivity analysis of the proportion of subjects who maintained vision at Week 52 (full analysis set)

	Ranibizumab	VEGF Trap-Eye		
	0.5Q4	2Q4	0.5Q4	2Q8
Last observation carried forward				
Subjects who maintained vision at Week 52 (%)	276 / 291 (94.85)	292 / 309 (94.50)	282 / 296 (95.27)	292 / 306 (95.42)
Difference (%) (95% CI)		0.35 (-3.25; 3.94)	-0.42 (-3.93; 3.08)	-0.58 (-4.03; 2.88)
Observed cases				
Subjects who maintained vision at Week 52 (%)	257 / 272 (94.49)	261 / 276 (94.57)	257 / 268 (95.90)	265 / 278 (95.32)
Difference (%) (95% CI)		-0.08 (-3.89; 3.73)	-1.41 (-5.02; 2.20)	-0.84 (-4.52; 2.84)
Worst observation carried forward				
Subjects who maintained vision at Week 52 (%)	274 / 291 (94.16)	290 / 309 (93.85)	282 / 296 (95.27)	292 / 306 (95.42)
Difference (%) (95% CI)		0.31 (-3.49; 4.11)	-1.11 (-4.73; 2.51)	-1.27 (-4.84; 2.30)
All drop-outs counted as non-responders				
Subjects who maintained vision at Week 52 (%)	260 / 291 (89.35)	266 / 309 (86.08)	262 / 296 (88.51)	271 / 306 (88.56)
Difference (%) (95% CI)		3.26 (-1.98; 8.50)	0.83 (-4.24; 5.91)	0.78 (-4.24; 5.81)
All treatment failures counted as non-responders				
Subjects who maintained vision at Week 52 (%)	272 / 291 (93.47)	287 / 309 (92.88)	278 / 296 (93.92)	288 / 306 (94.12)
Difference (%) (95% CI)		0.59 (-3.44; 4.63)	-0.45 (-4.38; 3.48)	-0.65 (-4.52; 3.23)

Note: Maintenance of vision was defined as a loss of < 15 letters in the ETDRS letter score
Difference is ranibizumab minus VEGF Trap-Eye; C.I. = confidence interval was calculated using a normal approximation.

The results for the additional efficacy outcome measures were:

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

There was no significant difference between the groups in:

- Proportion of subjects who lost 15 or more letters of vision ("moderate" vision loss) at Week 52
- Proportion of subjects who gained 30 or more letters of vision at Week 52
- Proportion of subjects who lost 30 or more letters of vision ("severe" vision loss) at Week 52
- Proportion of subjects who gained ≥ 0 letter of vision at Week 52
- Proportion of subjects who gained 10 or more letters of vision at Week 52
- Proportion of subjects with VA of 20/40 or better at Week 52

However, 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.

There was no significant between group differences in:

- Change from baseline in total lesion area as assessed by FA at Week 52
- Change from baseline in classic CNV area at Week 52

However, 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. There was no difference between the groups in change from baseline in area of fluorescein leakage as assessed by FA at Week 52. There was a decrease in CRT in the aflibercept 2 mg q4w group compared to ranibizumab: LS mean difference (95% CI) -10.60 (-21.1 to -0.09) p=0.047.

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. There was no significant difference in the EQ-5D.

Supportive efficacy data

StudyVGFT-OD-0702/14262

StudyVGFT-OD-0702/14262 was a single masked, randomised study conducted to compare long-term safety and tolerability of aflibercept in pre-filled syringes and vials. Subjects were eligible if they had neovascular AMD and completed dosing in *Study VGFT-OD-0502, Study VGFT-OD--0508, or Study VGFT-OD--0603.* The study treatments were aflibercept 2 mg PRN either as pre-filled syringe or as vials by intravitreal injection. The minimum time between treatments was 4 weeks. The aflibercept concentration was 40 mg/mL, hence the injection volume was 50 µL.

The efficacy outcome measures were:

- Change from baseline in ETDRS letters read
- Proportion of subjects who maintain vision (loss of <15 letters) from baseline
- Proportion of subjects with an increase of at least 15 letters from the baseline
- Frequency of treatment

The safety outcome measures were:

- AEs,
- Laboratory tests and
- IOP.

The study enrolled 157 subjects and of these,149 were randomised to treatment: 99 to pre-filled syringe and 50 to vial. A total of 132 subjects received at least one treatment. A total of 129 (82.2%) subjects completed the study: four (2.5%) withdrew because of AE and seven (4.5%) patients died. There were 93 (62.4%) females, 56 (37.6%) males and the age range was 55 to 93 years. The vial and pre-filled syringe groups were similar in demographic characteristics.

The median time to first re-injection was 112 days. Visual acuity was reduced from baseline but it is not clear whether the rate of decline was influenced by aflibercept (Figure 9). Vision was maintained to Week 136 by 132 (84.1%) subjects. Visual acuity decreased at the same rate in the vial and pre-filled syringe groups (Figure 10).

Figure 9. Mean Change in Visual Acuity (LOCF) from Baseline of This Study to the Cut-Off Date by Visit (All Enrolled Set).

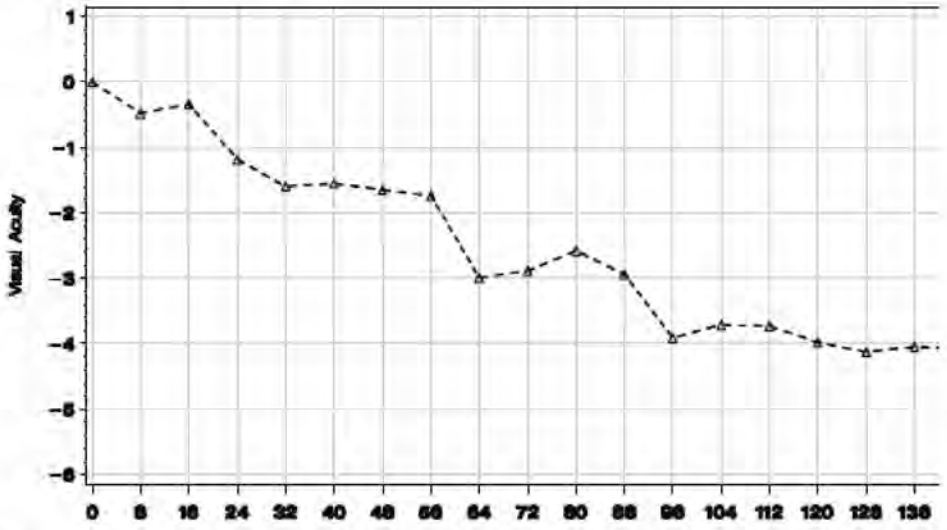
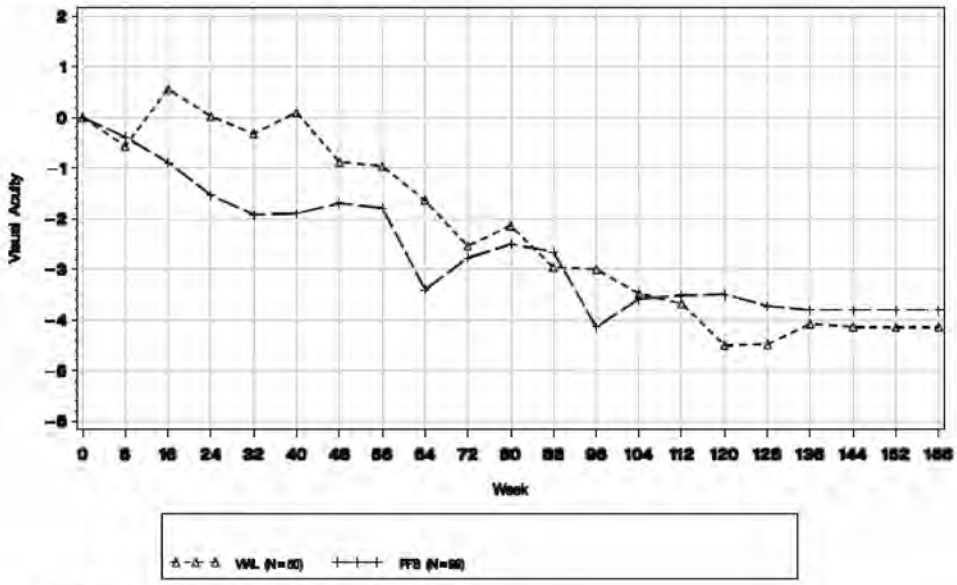


Figure 10. Mean Change in Visual Acuity (LOCF) from Baseline of This Study to the Cut-Off Date by Visit (All Randomized Set).



Study VGFT-OD-0706/13336 (DAVINCI)

Study VGFT-OD-0706/13336 (DAVINCI) was a double masked, randomised, parallel group, active controlled clinical trial of the efficacy and safety of aflibercept in subjects with DME. The study included subjects with clinically significant DME and central involvement defined as OCT central retinal thickness ≥250 µm; aged ≥18 years with Type 1 or 2 Diabetes Mellitus (DM); with ETDRS BCVA 20/40 to 20/320 (letter score of 73 to 24) in the study eye; and willing to use adequate contraception.

The study treatments were:

1. 1. Aflibercept 0.5 mg q4w
2. 2. Aflibercept 2 mg q4w
3. 3. Aflibercept 2 mg q8w
4. 4. Aflibercept 2 mg PRN
5. 5. Laser photocoagulation

Aflibercept was administered by intravitreal injection. The study duration was 52 weeks.

The primary efficacy outcome measure was the change in BCVA from baseline to Week 24. The secondary efficacy outcome measures were:

- The proportion of patients who gained at least 15 ETDRS letters in BCVA from baseline to Week 24
- Change from baseline in central retinal thickness at Week 24 as assessed by OCT
- The number of focal laser treatments through Week 24

The exploratory efficacy outcome measure was the change in central retinal sensitivity as measured by microperimetry.

The safety outcome measures were:

- AEs,
- Clinical laboratory tests,
- ECGs,
- Vital signs, and
- Ophthalmic examinations.

Hypothesis tests were performed using ANCOVA. The study was designed as a superiority study. The sample size calculation assumed a difference between laser and aflibercept in BCVA at 24 weeks to be 8 letters, with a SD of 10 for each group. In order to provide 84% power at an α of 0.0125 (to correct for four comparisons) 40 subjects would be required in each study group.

A total of 221 subjects were randomised and 219 of these received treatment: 44 with 0.5 mg aflibercept q4w, 44 with 2 mg q4w, 42 with 2 mg q8w, 45 with 2 mg PRN and 44 with laser photocoagulation. A total of 200 (90.5%) subjects completed the study; one discontinued due to AE and three patients died. There were 129 (58.9%) males, 90 (41.1%) females and the age range was 29 to 87 years. The treatment groups were similar in demographic characteristics.

All four aflibercept treatment groups were superior to laser treatment by the primary efficacy outcome measure. The mean change (SD) from baseline in BCVA was 8.6 (14.64) letters for aflibercept 0.5 mg q4w, 11.4 (8.67) for 2 mg q4w, 8.5 (7.50) for 2 mg q8w, 10.3 (7.52) for 2 mg PRN and 2.5 (16.14) for laser photocoagulation. There was no significant difference between the groups in the proportion of patients who gained at least 15 ETDRS letters in BCVA from baseline to Week 24. There was a greater decrease in CRT in the aflibercept groups than in the laser group: mean (SD) change from baseline -144.6 (110.65) µm for aflibercept 0.5 mg q4w, -194.5 (143.04) µm for 2 mg q4w, -127.3 (141.78) µm for 2 mg q8w, -153.3 (132.17) µm for 2 mg PRN, and -67.9 (135.17) µm for laser. In the laser group, most subjects had the maximum allowance of two treatments over the study period.

Evaluator's Overall Conclusions on Clinical Efficacy

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 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:

- In *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 compared to 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
- In *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 aflibercept 2 mg q4w: LS mean difference (95% CI) -1.61 (-3.19 to -0.04) p=0.045.

- In *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.
- In *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:

- In *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 compared to 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.
- In *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.

Safety

Introduction

Safety data were provided for the pharmacokinetic, pharmacodynamic and efficacy studies. In addition there was one study evaluable only for safety and limited safety data from three ongoing studies. The study evaluable only for safety was:

- Study VGFT-OD-0502/14395 Part B (CLEAR-IT 1)

The three ongoing studies (discussed below) were:

1. Study VGFT-OD-0910/14832
2. Study VGFT-OD-0819/14232 (COPERNICUS)
3. Study 14130 (GALILEO)

Study VGFT-OD-0502/14395 Part B (CLEAR-IT 1) was a randomised, double masked, active control Phase I study of safety, tolerability and initial bioeffect in subjects with neovascular AMD. The study was terminated after two of the planned 30 subjects were recruited. One subject was treated with VEGF Trap-eye,and the other with pegaptanib. The study treatments were:

4. VEGF Trap-Eye, 2 mg, one single injection followed by a sham injection 6 weeks later
5. Pegaptinib sodium, 0.3 mg, two injections 6 weeks apart

There was a double masked phase of 57 days duration followed by an open label phase of up to 12 months where VEGF Trap-Eye, 4 mg was administered on a PRN basis. Treatments were administered by intravitreal injection. Efficacy outcome measures were not reported.

The safety outcome measures were:

- AEs
- Laboratory measures and
- Anti-VEGF Trap antibodies.

Patient exposure

Study VGFT-OD-0502/14395 Part A (CLEAR-IT 1), a total of 21 subjects were exposed to doses of aflibercept ranging from 0.05 mg to 4.0 mg. Twelve subjects received a single dose and nine subjects received additional doses of 4.0 mg in the open label phase, up to 10 doses.

Study VGFT-OD-0502/14395 Part B (CLEAR-IT 1), one subject was treated with VEGF Trap-Eye 2 mg on one occasion and 4 mg on five occasions. The other subject was treated with VEGF Trap-Eye 4 mg on two occasions.

Study VGFT-OD-0502/14395 Part C (CLEAR-IT 1), 28 subjects were exposed to VEGF Trap-Eye for a range of 0.15 mg to 60.15 mg and the total number of injections ranged from 1 to 16.

Study VGFT-OD-0603/14396 (CLEAR-IT 1b), twenty subjects were exposed to 4 mg VEGF-Trap for one to twelve doses.

Study VGFT-OD-0512/14805 (CLEAR-IT DME 1), five subjects with DME were treated with a single intravitreal administration of VEGF Trap-Eye 4 mg in 100µL volume.

Study VGFT-OD-0305, exposure to intravenous VEGF Trap was: seven subjects exposed to 0.3 mg/kg for two to four doses; seven exposed to 1.0 mg/kg for one to four doses and five exposed to 3.0 mg/kg for one to two doses.

Study VGFT-OD-0306, four subjects received one to eight doses of 0.3 mg/kg and three subjects received one to three doses of 1 mg/kg.

Study VGFT-OD-0307, six subjects received four doses of VEGF Trap 0.3 mg/kg intravenously.

Study PDY6655, 40 subjects were exposed to a single injection of 2.0 mg/kg aflibercept subcutaneously and of these, 38 were also exposed to 2.0 mg/kg intravenously.

Study PDY6656, 36 subjects were exposed to a single dose of intravenous aflibercept: twelve were treated with 1 mg/kg, twelve with 2 mg/kg, and twelve with 4 mg/kg.

Study VGFT-OD-0508/14394 (CLEAR-IT AMD-2), 32 subjects were exposed to 0.5 mg q4w for one to 13 doses; 32 subjects to 0.5 mg q12w for one to seven doses; 31 subjects to 2 mg q12w for three to eight doses; 31 subjects to 2 mg q12h for one to eight doses; and 31 subjects to 4 mg q12h for one to nine doses.

Study VGFT-OD-0605/14393 (VIEW 1), 304 subjects were treated with aflibercept 2 mg q4w for a median of 13 treatments, 304 subjects with 0.5 mg q4w for a median of 13 treatments and 303 subjects with 2 mg q8w for a median of 8 treatments.

Study 311523 (VIEW 2), 309 subjects were exposed to aflibercept 2 mg q4w, 297 subjects to 0.5 mg q4w, 307 subjects to 2 mg q8w and 291 subjects to ranibizumab. Thirteen injections (including, where allocated, sham injections) were received by 237 (76.7%) subjects in the aflibercept 2 mg q4w group, 238 (80.1%) in the 0.5 mg q4w group, 287 (93.5%) in the 2 mg q8w group and 280 (96.2%) in the ranibizumab group. Thirteen injections would correspond with 52 weeks exposure for each treatment.

StudyVGFT-OD-0702/14262, 132 subjects were exposed to aflibercept 2 mg by intravitreal injection; 112 subjects were exposed for more than 24 weeks.

Study VGFT-OD-0706/13336 (DAVINCI), to Week 20, 44 subjects were exposed to 0.5 mg aflibercept by intravitreal injection, with 33 subjects exposed to six injections, and 131 subjects were exposed to 2 mg with 42 subjects exposed to six injections.

Adverse events

Study VGFT-OD-0502/14395 Part A, ocular TEAEs were reported in the treated eye by 18 (85.7%) subjects and in the fellow eye by 14 (66.7%). There was an excess of pain and reduced visual acuity in the treated eye. During the open label extension six (66.7%) subjects reported TEAEs: three (33.3%) reported increased intraocular pressure, two (22.2%) eye pain and two (22.2%) vitreous detachment. There was a mean (SD) increase in intraocular pressure of 4.3 (3.89) mmHg 30 minutes postdose.

Study VGFT-OD-0502/14395 Part B, during the double blind phase the subject treated with VEGF Trap-Eye had conjunctival hyperaemia, retinal haemorrhage and increased IOP (increase of 17 mmHg post dose). The subject treated with pegaptinib had conjunctival hyperaemia. During the open label phase one subject had episodes of refractive disorder, and one subject had vitreous floaters.

Study VGFT-OD-0502/14395 Part C, ten (71.4%) subjects in each treatment group reported TEAEs that were associated with the study eye. Four (28.6%) subjects in each group reported TEAEs associated with the fellow eye. The excess of TEAEs in the study eye was attributable to more subjects with conjunctival haemorrhage, refractive disorder and decreased visual acuity. Seventeen (77.3%) subjects had study eye TEAEs during the open-label extension. The most frequent study eye TEAEs were conjunctival hemorrhage in four (18.2%) subjects, increased IOP in four (18.2%) subjects, eye pain in three (13.6%) subjects, reduced VA in three (13.6%) subjects and vitreous floaters in three (13.6%) subjects.

Study VGFT-OD-0603, 15 (75%) subjects reported non-ocular TEAEs. The most commonly reported TEAE was nasopharyngitis in four (20%) subjects. Ocular TEAEs were reported in 19 (95%) subjects in the treated eye and nine (45%) in the fellow eye. There was an excess of subjects with conjunctival haemorrhage, eye irritation and eye pain in the treated eye compared with the fellow eye (Tables 12 and 13). There was no apparent difference between the treatment groups or the 50 μL and 100 μL injection sizes in IOP (Table 14).

Table 12. Number of Patients who Reported Ocular Treatment-emergent Adverse Events in the Study Eye by SOC and PT

MedDRA v10.0 System Organ Class	Double-masked cohort		Open label cohort	All
Preferred Term	4 mg ITV-1 (100 µL) N=6	4 mg ITV-2 (100 µL) N=6	4 mg ITV-2 (50 µL) N=8	N=20
Any Ocular AE	6(100%)	5(83.3%)	8(100%)	19(95%)
Eye disorders	**6(100%)**	**5(83.3%)**	**6(75%)**	**17(85%)**
Conjunctival haemorrhage	3(50%)	2(33.3%)	4(50%)	9(45%)
Eye irritation	4(66.7%)	3(50%)	2(25%)	9(45%)
Eye pain	2(33.3%)		3(37.5%)	5(25%)
Vitreous floaters	1(16.7%)	1(16.7%)	2(25%)	4(20%)
Vision blurred	2(33.3%)			2(10%)
Visual acuity reduced	1(16.7%)		1(12.5%)	2(10%)
Anterior chamber cell		1(16.7%)		1(5%)
Blepharitis	1(16.7%)			1(5%)
Cataract	1(16.7%)			1(5%)
Cataract subcapsular	1(16.7%)			1(5%)
Eye haemorrhage			1(12.5%)	1(5%)
Eyelids pruritus	1(16.7%)			1(5%)
Macular degeneration	1(16.7%)			1(5%)
Photopsia			1(12.5%)	1(5%)
Retinal artery occlusion	1(16.7%)			1(5%)
Retinal haemorrhage		1(16.7%)		1(5%)
Retinal vascular disorder	1(16.7%)			1(5%)
Visual disturbance	1(16.7%)			1(5%)
Vitreous detachment			1(12.5%)	1(5%)
Injury, poisoning and procedural complication	**0(0.0%)**	**0(0.0%)**	**3(37.5%)**	**3(15%)**
Incorrect dose administered			3(37.5%)	3(15%)
Investigations	**2(33.3%)**	**0(0.0%)**	**0(0.0%)**	**2(10%)**
Intraocular pressure increased	2(33.3%)			2(10%)

Table 13. Number of Patients who reported Ocular Treatment-emergent Adverse Events in the Fellow Eye by SOC and PT.

MedDRA v10.0 System Organ Class	Double-masked cohort		Open label cohort	All
Preferred Term	4 mg ITV-1 (100 µL) N=6	4 mg ITV-2 (100 µL) N=6	4 mg ITV-2 (50 µL) N=8	N=20
Any Ocular AE	4(66.7%)	2(33.3%)	3(37.5%)	9(45%)
Eye disorders	**4(66.7%)**	**2(33.3%)**	**3(37.5%)**	**9(45%)**
Macular degeneration	1(16.7%)		1(12.5%)	2(10%)
Macular oedema		1(16.7%)	1(12.5%)	2(10%)
Blepharitis	1(16.7%)			1(5%)
Conjunctival haemorrhage			1(12.5%)	1(5%)
Detachment of retinal pigment epithelium		1(16.7%)		1(5%)
Retinal artery embolism	1(16.7%)			1(5%)
Retinal exudates			1(12.5%)	1(5%)
Retinal oedema		1(16.7%)		1(5%)
Vision blurred		1(16.7%)		1(5%)
Vitreous detachment			1(12.5%)	1(5%)
Vitreous floaters	1(16.7%)			1(5%)

Table 14. Baseline Values and Change from Baseline in Pre-dose IOP (mmHg) to Weeks 1, 4, 8, and 12.

Study Week	Statistic	Double-masked cohort		Open label cohort
		4 mg ITV-1 (100 µL) N=6	4 mg ITV-2 (100 µL) N=6	4 mg ITV-2 (50 µL) N=8
Baseline	**n**	**6**	**6**	**8**
	Mean (SD)	15(2.83)	13.7(2.94)	14.8(2.76)
	Median	15	13.5	15
	(min:max)	(11 : 18)	(11 : 19)	(10 : 18)
Week 1	**n**	**6**	**6**	**8**
	Mean (SD)	-1(1.9)	-0.8(2.71)	-0.6(3.11)
	Median	-1	0	0
	(min:max)	(-4 : 1)	(-6 : 2)	(-8 : 2)
Week 4	**n**	**6**	**5**	**9**
	Mean (SD)	-3.2(3.82)	-1(3.81)	0.7(2.65)
	Median	-4	0	2
	(min:max)	(-8 : 3)	(-7 : 3)	(-3 : 4)
Week 8	**n**	**6**	**5**	**8**
	Mean (SD)	-3.3(2.07)	-3.4(6.11)	-0.8(3.41)
	Median	-3.5	0	-0.5
	(min:max)	(-6 : -1)	(-13 : 1)	(-6 : 4)
Week 12	**n**	**6**	**5**	**8**
	Mean (SD)	-2.5(4.09)	-2.2(4.15)	-1.5(3.82)
	Median	-3.5	-2	-0.5
	(min:max)	(-8 : 4)	(-9 : 2)	(-7 : 2)

Study VGFT-OD-0512, four subjects reported TEAEs affecting the study eye: conjunctival haemorrhage in three subjects. Four subjects reported systemic TEAEs: infection in two subjects.

Study VGFT-OD-0305, non-ocular TEAEs were reported in all subjects in the VEGF trap groups and 4 (66.7%) subjects in the placebo (Table 15). The most commonly reported TEAEs were: headache, hypertension, and proteinuria. VEGF Trap was associated with an increase in mean diastolic blood pressure. There did not appear to be an excess of ocular AEs in the VEGF Trap treatment groups.

Table 15. Most Common Non-Ocular AEs

Preferred Term: n (%)	Pooled Placebo (6)	Dose of VEGF Trap			Active Groups Combined (19)
		0.3 mg/kg (7)	1.0 mg/kg (7)	3.0 mg/kg (5)	
Headache	0 (0)	1 (14.3)	3 (42.9)	4 (80.0)	8 (42.1)
Hypertension	0 (0)	0 (0)	3 (42.9)	3 (60.0)	6 (31.6)
Proteinuria	0 (0)	0 (0)	2 (28.6)	3 (60.0)	5 (26.3)
Hoarseness	1 (16.7)	0 (0)	2 (28.6)	3 (60.0)	5 (26.3)
Arthralgia	1 (16.7)	1 (14.3)	1(14.3)	2 (40.0)	4 (21.1)
Cough	1 (16.7)	1 (14.3)	2 (28.6)	0 (0)	3 (15.8)
Aggravation of Arthritis Pain	0 (0)	0 (0)	0 (0)	3 (60)	3 (15.8)

Study VGFT-OD-0306, a total of 29 non-ocular TEAEs were reported in seven subjects. The most commonly reported TEAE was dysphonia in two subjects. A total of five ocular TEAEs were reported in two subjects. The most commonly reported ocular TEAE was reduced visual acuity in both subjects.

Study VGFT-OD-0307, all subjects (six VEGF Trap and three placebo) reported at least one TEAE. The most commonly reported TEAEs were: hypoglycemia (3), arthralgia (2), back pain (2) and proteinuria (2). There were no dose limiting toxicities.

Study PDY6655, 132 TEAEs were reported in 36 (94.7%) subjects after intravenous administration and 159 in 34 (85.0%) after subcutaneous. Twelve injection site reactions were reported with intravenous and six with subcutaneous (Table 16). The most commonly reported TEAEs were headache, acneform dermatitis and gastroenteritis (Table 16). No prolonged QTc[12] interval >450 ms and QTc interval increases from baseline (>60 ms) were reported irrespective of the route of administration.

Study PDY6656, a total of 30 TEAEs were reported in ten (83.3%) subjects in the 1 mg/kg group, 44 in eleven (91.7%) in the 2 mg/kg group, 48 in eleven (91.7%) in the 4 mg/kg group and 23 in ten (83.3%) in the placebo group. The incidence of headache appeared to be dose related and the incidence of dysphonia was increased in the aflibercept groups.

Study VGFT-OD-0508, systemic TEAEs were reported in 27 (84.45) subjects in the 0.5 mg q4w group, 25 (78.1%) in the 0.5 mg q12w group, 28 (90.3%) in the 2 mg q4w group, 24 (77.4%) in the 2 mg q12w group and 25 (80.6%) in the 4 mg q12w group. The commonest TEAEs were infections and there did not appear to be any dose related TEAEs. Ocular TEAEs in the study eye were reported in 29 (90.6%) subjects in the 0.5 mg q4w group, 26 (81.3%) in the 0.5 mg q12w group, 26 (83.9%) in the 2 mg q4w group, 25 (80.6%) in the 2 mg q12h group and 28 (90.3%) in the 4 mg q12h group. The commonest TEAE in the study eye was conjunctival haemorrhage which did not appear to be related to either dose or frequency of administration (Table 17). There was no clinically significant change in mean blood pressure values. There was a mean (SD) increase in IOP of 3.2 (5.05) mmHg the day after intravitreal injection that did not increase

[12] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval QTc is often calculated.

following subsequent treatments. Seven subjects had treatment emergent clinically significant ECG abnormalities but none appeared to be treatment related.

Table 16. Summary of treatment-emergent adverse events. Safety population

Primary System Organ Class Preferred term	AVE0005 2.0 mg/kg I.V. (N=38) n (%)		AVE0005 2.0 mg/kg S.C. (N=40) n (%)	
Any class	36	(94.7)	34	(85.0)
Infections and infestations	16	(42.1)	17	(42.5)
Bronchitis	1	(2.6)	2	(5.0)
Gastroenteritis	10	(26.3)	10	(25.0)
Hordeolum	1	(2.6)	0	(0)
Influenza	1	(2.6)	1	(2.5)
Nasopharyngitis	3	(7.9)	2	(5.0)
Oral herpes	3	(7.9)	1	(2.5)
Pharyngitis	1	(2.6)	2	(5.0)
Rhinitis	0	(0)	1	(2.5)
Sinusitis	0	(0)	1	(2.5)
Tinea versicolour	0	(0)	1	(2.5)
Upper respiratory tract infection	0	(0)	1	(2.5)
Urinary tract infection	0	(0)	2	(5.0)
Immune system disorders	1	(2.6)	0	(0)
Allergy to arthropod bite	1	(2.6)	0	(0)
Nervous system disorders	17	(44.7)	18	(45.0)
Headache	16	(42.1)	17	(42.5)
Paraesthesia	1	(2.6)	2	(5.0)
Eye disorders	0	(0)	1	(2.5)
Conjunctivitis	0	(0)	1	(2.5)
Ear and labyrinth disorders	0	(0)	1	(2.5)
Vertigo	0	(0)	1	(2.5)
Cardiac disorders	1	(2.6)	0	(0)
Palpitations	1	(2.6)	0	(0)
Vascular disorders	1	(2.6)	0	(0)
Orthostatic hypotension	1	(2.6)	0	(0)
Respiratory, thoracic and mediastinal disorders	10	(26.3)	7	(17.5)
Dysphonia	4	(10.5)	5	(12.5)
Epistaxis	4	(10.5)	1	(2.5)
Pharyngolaryngeal pain	1	(2.6)	1	(2.5)
Rhinitis allergic	2	(5.3)	1	(2.5)
Gastrointestinal disorders	10	(26.3)	15	(37.5)
Abdominal pain	2	(5.3)	1	(2.5)
Aphthous stomatitis	0	(0)	1	(2.5)
Constipation	1	(2.6)	3	(7.5)
Dental caries	1	(2.6)	1	(2.5)
Diarrhoea	1	(2.6)	4	(10.0)
Dyspepsia	3	(7.9)	1	(2.5)
Flatulence	0	(0)	1	(2.5)
Glossitis	1	(2.6)	0	(0)
Nausea	3	(7.9)	6	(15.0)
Periodontitis	0	(0)	1	(2.5)
Stomatitis	1	(2.6)	0	(0)
Vomiting	2	(5.3)	1	(2.5)

Table 17. Number of Patients (%) with Ocular TEAEs in the Study Eye by Preferred Term as Reported by ≥2% of Patients

MedDRA v10.0 Preferred Term	0.5mg q4	0.5mg q12	2mg q4	2mg q12	4mg q12	All
	N=32	N=32	N=31	N=31	N=31	N=157
Any Ocular TEAE in the Study Eye	29(90.6)	26(81.3)	26(83.9)	25(80.6)	28(90.3)	134(85.4)
Conjunctival Haemorrhage	11(34.4)	12(37.5)	9(29.0)	15(48.4)	13(41.9)	60(38.2)
Intraocular Pressure Increased	10(31.3)	4(12.5)	6(19.4)	3(9.7)	7(22.6)	30(19.1)
Refraction Disorder	4(12.5)	7(21.9)	5(16.1)	3(9.7)	7(22.6)	26(16.6)
Retinal Haemorrhage	7(21.9)	6(18.8)	2(6.5)	5(16.1)	3(9.7)	23(14.6)
Visual Acuity Reduced	5(15.6)	6(18.8)	2(6.5)	6(19.4)	2(6.5)	21(13.4)
Vitreous Detachment	4(12.5)	2(6.3)	3(9.7)	5(16.1)	4(12.9)	18(11.5)
Eye Pain	5(15.6)	2(6.3)	4(12.9)	1(3.2)	4(12.9)	16(10.2)
Vitreous Floaters	3(9.4)	3(9.4)	2(6.5)	4(12.9)	2(6.5)	14(8.9)
Detachment Of Retinal Pigment Epithelium	1(3.1)	2(6.3)	4(12.9)	4(12.9)	1(3.2)	12(7.6)
Blepharitis	3(9.4)	0	3(9.7)	3(9.7)	1(3.2)	10(6.4)
Retinal Oedema	2(6.3)	2(6.3)	2(6.5)	2(6.5)	2(6.5)	10(6.4)
Cataract	1(3.1)	2(6.3)	0	2(6.5)	3(9.7)	8(5.1)
Subretinal Fibrosis	2(6.3)	1(3.1)	1(3.2)	2(6.5)	2(6.5)	8(5.1)
Visual Disturbance	2(6.3)	1(3.1)	0	2(6.5)	3(9.7)	8(5.1)
Cataract Nuclear	3(9.4)	0	4(12.9)	0	0	7(4.5)
Dry Eye	3(9.4)	0	2(6.5)	2(6.5)	0	7(4.5)
Eye Irritation	5(15.6)	0	1(3.2)	0	1(3.2)	7(4.5)
Retinal Pigment Epitheliopathy	0	2(6.3)	1(3.2)	3(9.7)	1(3.2)	7(4.5)
Cataract Subcapsular	1(3.1)	1(3.1)	1(3.2)	1(3.2)	2(6.5)	6(3.8)
Photopsia	1(3.1)	0	0	2(6.5)	3(9.7)	6(3.8)
Lacrimation Increased	1(3.1)	1(3.1)	1(3.2)	0	2(6.5)	5(3.2)
Punctate Keratitis	0	0	1(3.2)	2(6.5)	2(6.5)	5(3.2)
Eye Inflammation	2(6.3)	0	0	1(3.2)	1(3.2)	4(2.5)
Foreign Body Sensation In Eyes	3(9.4)	0	1(3.2)	0	0	4(2.5)
Maculopathy	1(3.1)	0	0	2(6.5)	1(3.2)	4(2.5)

Study VGFT-OD-0605/14393 (VIEW 1), non-ocular TEAEs were reported in 220 (72.4%) subjects in the aflibercept 2 mg q4w group, 231 (76.0%) in the 0.5 mg q4w group, 223 (73.6%) in the 2 mg q8w group and 234 (77.0%) in the ranibizumab group. Infections were the most common TEAEs and the pattern of TEAEs was similar for all four treatment groups. Ocular TEAEs in the study eye were reported in 228 (75.0%) subjects in the aflibercept 2 mg q4w group, 226 (74.3%) in the 0.5 mg q4w group, 238 (78.5%) in the 2 mg q8w group and 246 (80.9%) in the ranibizumab group. Conjunctival haemorrhage was the most common TEAE in the study eye and the patterns were similar for the treatment groups. Pre-injection IOP decreased from baseline by approximately 0.2 mmHg in the aflibercept groups but remained at baseline levels in the ranibizumab. Ocular TEAEs in the fellow eye were reported in 151 (49.7%) subjects in the aflibercept 2 mg q4w group, 151 (49.7%) in the 0.5 mg q4w group, 143 (47.2%) in the 2 mg q8w group and 150 (49.3%) in the ranibizumab group. The commonest injection related TEAE was conjunctival haemorrhage, occurring in 105 (34.5%) subjects in the 2 mg q4w group, 117 (38.5%) in the 0.5 mg q4w group, 127 (41.9%) in the 2 mg q8w group and 140 (46.1%) in the ranibizumab group. Hypertension was reported in 21 (6.9%) subjects in the aflibercept 2 mg q4w group, 21 (6.9%) in the 0.5 mg q4w group, 20 (6.6%) in the 2 mg q8w group and 25 (8.2%) in the ranibizumab group. Arterial thromboembolic events were reported in two (0.7%)

subjects in the aflibercept 2 mg q4w group, seven (2.3%) in the 0.5 mg q4w group, six (2.0%) in the 2 mg q8w group and five (1.6%) in the ranibizumab group.

Study 311523 (VIEW 2), TEAEs were reported in 277 (89.6%) subjects in the aflibercept 2 mg q4w group, 262 (88.2%) in the 0.5 mg q4w group, 277 (90.2%) in the 2 mg q8w group and 250 (85.9%) in the ranibizumab group. Ocular TEAEs in the study eye were reported in 191 (61.8%) subjects in the aflibercept 2 mg q4w group, 182 (61.3%) in the 0.5 mg q4w group, 198 (64.5%) in the 2 mg q8w group and 187 (64.3%) in the ranibizumab group. The commonest ocular TEAEs in the study eye were reduced visual acuity and conjunctival haemorrhage (Table 18). Ocular TEAEs in the fellow eye were reported in 110 (35.6%) subjects in the aflibercept 2 mg q4w group, 118 (39.7%) in the 0.5 mg q4w group, 123 (40.1%) in the 2 mg q8w group and 124 (42.6%) in the ranibizumab group. Non-ocular TEAEs were reported in 231 (74.8%) subjects in the aflibercept 2 mg q4w group, 206 (69.4%) in the 0.5 mg q4w group, 213 (69.4%) in the 2 mg q8w group and 181 (62.2%) in the ranibizumab group. The commonest non-ocular TEAEs were nasopharyngitis (6.4%) and influenza (4.3%). Arterial thromboembolic events were reported in eight (2.6%) subjects in the aflibercept 2 mg q4w group, eight (2.7%) in the 0.5 mg q4w group, eight (2.6%) in the 2 mg q8w group and six (2.1%) in the ranibizumab group. Hypertension was reported in 31 (10.0%) subjects in the aflibercept 2 mg q4w group, 22 (7.4%) in the 0.5 mg q4w group, 28 (9.1%) in the 2 mg q8w group and 29 (10.0%) in the ranibizumab group. Pre-injection mean IOP increased slightly in the ranibizumab group and decreased slightly in the aflibercept groups (Table 18). There were no clinically significant changes in mean vital sign or ECG parameters.

Table 18. Ocular TEAEs in the study eye occurring in ≥5.0% of the subjects in any treatment group (Safety analysis set).

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 ocular TEAE (study eye)	187 (64.3)	191 (61.8)	182 (61.3)	198 (64.5)	571 (62.5)
Visual acuity reduced	20 (6.9)	26 (8.4)	34 (11.4)	33 (10.7)	93 (10.2)
Conjunctival haemorrhage	23 (7.9)	24 (7.8)	37 (12.5)	30 (9.8)	91 (10.0)
Retinal haemorrhage	29 (10.0)	27 (8.7)	30 (10.1)	27 (8.8)	84 (9.2)
Macular degeneration	23 (7.9)	27 (8.7)	23 (7.7)	30 (9.8)	80 (8.8)
Eye pain	27 (9.3)	33 (10.7)	22 (7.4)	21 (6.8)	76 (8.3)
Intraocular pressure increased	19 (6.5)	24 (7.8)	15 (5.1)	15 (4.9)	54 (5.9)
Detachment of retinal pigment epithelium	15 (5.2)	18 (5.8)	15 (5.1)	12 (3.9)	45 (4.9)
Vitreous detachment	9 (3.1)	18 (5.8)	9 (3.0)	15 (4.9)	42 (4.6)
Cataract	15 (5.2)	16 (5.2)	12 (4.0)	12 (3.9)	40 (4.4)
Ocular hyperaemia	18 (6.2)	12 (3.9)	13 (4.4)	9 (2.9)	34 (3.7)
Retinal degeneration	11 (3.8)	17 (5.5)	9 (3.0)	7 (2.3)	33 (3.6)

Note: Preferred terms are sorted in descending order by frequency in the VEGF Trap-Eye combined group.

StudyVGFT-OD-0702/14262, TEAEs were reported by 154 (98.1%) subjects. There was a lower rate of AEs in subjects treated with the pre-filled syringes: 93 (93.9%) subjects compared with 50 (100%) subjects in the vial group (Table 19). Ocular AEs were reported in 134 (85.4%) subjects. The most commonly reported ocular AEs were: cataract in 23 (14.6%) subjects, conjunctival haemorrhage in 23 (14.6%) subjects, 'visual acuity reduced' in 23 (14.6%) subjects and retinal haemorrhage in 20 (12.7%) subjects. Ocular AEs were more common in the vial group than in the pre-filled syringe (Table 20). Non-ocular AEs were reported in 148 (94.3%) subjects and the pattern of AEs is as would be expected for the age group. The most common injection related AEs were: conjunctival hemorrhage in 20 (13%) subjects, eye pain in eight (5%) subjects and injection site pain in seven (5%) subjects. One subject had an increase in IOP ≥10 mmHg.

Table 19. Overall Adverse Event Profile (All Randomized Set)

	Vial (N=50) n (%)		PFS (N=99) n (%)		Total (N=149) n (%)	
Subjects with Events	**Pre Randomization**	**Post Randomization**	**Pre Randomization**	**Post Randomization**	**Pre Randomization**	**Post Randomization**
No. of Subjects with Events, n (%)	41 (82.0)	50 (100)	82 (82.8)	93 (93.9)	123 (82.6)	143 (96.0)
Ocular AEs	29 (58.0)	42 (84.0)	63 (63.6)	71 (71.7)	92 (61.7)	113 (75.8)
Study eye	23 (46.0)	38 (76.0)	55 (55.6)	58 (58.6)	78 (52.3)	96 (64.4)
Fellow eye	20 (40.0)	35 (70.0)	43 (43.4)	50 (50.5)	63 (42.3)	85 (57.0)
Non-Ocular AEs	33 (66.0)	44 (88.0)	65 (65.7)	87 (87.9)	98 (65.8)	131 (87.9)
Drug-Related AEs	1 (2.0)	0	1 (1.0)	1 (1.0)	2 (1.3)	1 (0.7)
Ocular drug-related AEs	1 (2.0)	0	1 (1.0)	0	2 (1.3)	0
Study eye	1 (2.0)	0	1 (1.0)	0	2 (1.3)	0
Fellow eye	0	0	0	0	0	0
Non-Ocular drug-related AEs	0	0	0	1 (1.0)	0	1 (0.7)
Maximum Intensity of Ocular AEs						
Mild	23 (46.0)	39 (78.0)	56 (56.6)	65 (65.7)	79 (53.0)	104 (69.8)
Moderate	11 (22.0)	12 (24.0)	27 (27.3)	27 (27.3)	38 (25.5)	39 (26.2)
Severe	1 (2.0)	3 (6.0)	3 (3.0)	5 (5.1)	4 (2.7)	8 (5.4)
Study eye	1 (2.0)	2 (4.0)	2 (2.0)	4 (4.0)	3 (2.0)	6 (4.0)
Fellow eye	0	2 (4.0)	1 (1.0)	1 (1.0)	1 (0.7)	3 (2.0)
Maximum Intensity of Non-Ocular AEs						
Mild	22 (44.0)	39 (78.0)	55 (55.6)	77 (77.8)	77 (51.7)	116 (77.9)
Moderate	19 (38.0)	17 (34.0)	32 (32.3)	55 (55.6)	51 (34.2)	72 (48.3)
Severe	5 (10.0)	12 (24.0)	6 (6.1)	16 (16.2)	11 (7.4)	28 (18.8)
SAEs	9 (18.0)	16 (32.0)	13 (13.1)	33 (33.3)	22 (14.8)	49 (32.9)
Injection-related SAEs	1 (2.0)	0	0	1 (1.0)	1 (0.7)	1 (0.7)
AEs Leading to Withdrawal from Study	0	2 (4.0)	0	1 (1.0)	0	3 (2.0)
Discontinuation of Study Drug due to AEs	0	1 (2.0)	0	2 (2.0)	0	3 (2.0)
Death due to AE	0	2 (4.0)	0	3 (3.0)	0	5 (3.4)