CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s000

MEDICAL REVIEW(S)

Medical Officer's Review #2 of BLA 125-387

Established name:	aflibercept
Trade name:	Eylea
Therapeutic class:	anti-VEGF
Applicant:	Regeneron
Dosing regimen:	Intravitreal injection
Indication:	EYLEA (aflibercept) is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD)

Background:
The original PDUFA date for BLA 125-387 was 8/18/11. The PDUFA date was extended to 11/18/11 to resolve Product Quality and Micro Sterility outstanding issues. The safety and efficacy from my original review are unchanged. Attached is the final label.

Recommendation:
BLA 125-387 is recommended for approval with the attached labeling.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Signatures:

Reviewer Signature _____ 11/18/11
Sonal D. Wadhwa, MD

Clinical Team Leader Signature _____ 11/18/11 Concurrence Yes ___ No ___
William Boyd, MD

Deputy Division Director Review BLA 125387

Date	November 10, 2011
From	Wiley A. Chambers, MD
BLA #	125387
Applicant	Regeneron Pharmaceuticals, Inc.
Date of Original Submission	February 18, 2011
Name	Eylea (aflibercept)
Strength/Dosage form Route of Administration	40 mg/mL solution for intravitreal injection
Proposed Indication(s)	Treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD)
Recommended:	Recommended for Approval

1. Introduction

AMD is a leading cause of blindness in developed countries. Neovascular (Wet) AMD is due to proliferation of abnormal blood vessels behind the retina. These blood vessels leak blood and fluid into the retina, which results in visual abnormalities. The development of these abnormal blood vessels is due in part to the activity of VEGF (vascular endothelial growth factor), and its inhibition is expected to impact on the onset and/or severity of vision loss associated with the proliferation of abnormal blood vessels. Eylea (aflibercept), also known as aflibercept injection or VEGF Trap is a recombinant protein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to an IgG1 Fc. VEGF Trap is a specific antagonist that binds and inactivates circulating VEGF and PlGF (placental growth factor 1). In comparison to previously approved treatments for neovascular AMD, pegaptanib (Macugen) is an inhibitor of the VEGF165 isomer and ranibizumab (Lucentis) is an inhibitors of multiple VEGF-A isomers.

Products used clinically for this proposed indication are:

NDA/BLA	Drug	Approval	Indication
NDA 21-119	Photodynamic therapy (PDT)/ Verteporfin	April 2000	Indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to AMD, pathologic myopia, or POHS.
NDA 21-756	Macugen (pegaptanib injection)	December 2004	Indicated for the treatment of neovascular (wet) age-related macular degeneration
	Avastin (bevacizumab)	Used, but not approved for this indication	
BLA 125-156	Lucentis (ranibizumab injection)	June 2006	Indicated for the treatment of patients with neovascular (wet) age-related macular Degeneration

2. Background

IND 12,462 for VEGF Trap-Eye for the treatment of wet AMD was opened on June 15, 2005.

On June 1, 2009, a Type C meeting (telecon) was held to discuss Regeneron's Pharmacology/Toxicology program for treatment of AMD (IND 12,462) [redacted] (b) (4) On September 15, 2009, a Type C meeting (telecon) was held to discuss the status of/ development plans for Regeneron's [redacted] (b) (4) for treatment of age-related macular degeneration (AMD).

On September 8, 2010, a preBLA Clinical meeting was held to discuss clinical, clinical pharmacology, statistical, and regulatory issues concerning the upcoming BLA submission for treatment of AMD. On September 27, 2010, a preBLA CMC meeting was held to discuss plans for Regeneron's submission of the BLA for treatment of AMD.

On June 17, 2011, the FDA Dermatologic and Ophthalmic Drug Advisory Committee reviewed BLA 125387 and unanimously agreed that adequate safety and efficacy for aflibercept injection had been demonstrated for the treatment of neovascular age-related macular degeneration.

3. Product Quality

Description: Intravitreal injection (solution), 40 mg/mL. Vascular endothelial growth factor receptor type VEGFR (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer. The Fc portion of human IgG1 is fused to human vascular endothelial growth factor receptor (VEGFR)-derived peptide domains. VEGFR2 extracellular Ig domain 3 is fused to the Fc region, and VEGFR1 extracellular Ig domain 2 is fused to the VEGFR2 domain. [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) The theoretical (unglycosylated) molecular weight is 96.9 kD, and the experimental molecular weight is 115 kD. The isoelectric point is 5.8-8.3. Potency is defined as IC_{50} of the sample relative to IC_{50} of the reference standard in a proprietary VEGF-stimulated reporter gene assay. Proposed dating period for the drug product is [redacted] (b) (4) when stored at 2-8°C.

The application originally proposed [redacted] (b) (4) (vials [redacted] (b) (4)) [redacted] (b) (4) 40 mg/mL). All, but one vial of one strength (40 mg/mL) of the configurations have been withdrawn from the current application.

INSPECTIONS

A pre-approval inspection (PAI) for aflibercept drug substance production at the [redacted] (b) (4) facility was conducted from [redacted] (b) (4). [redacted] (b) (4) is responsible for manufacture of the drug substance intermediate, drug substance, and formulated bulk and for QC testing. A form 483 was issued at the end of this inspection. Observations made during the

inspection pertain to inadequate microbial control strategy for (b) (4) manufacture of aflibercept drug substance and QA documents that do not assure appropriate production record review and release of commercial material. This inspection was initially classified VAI; however, final classification is pending finalization of the review by CDER OC.

The Product Quality Reviewer and review group has resolved multiple deficiencies originally identified in the application. A number of post-approval commitments have been made to re-evaluate procedures and specifications after there is additional experience in manufacturing of the product.

4. Nonclinical Pharmacology/Toxicology

As presented in the Pharmacology/Toxicology review: The monkey was considered as the relevant species. Findings observed in ocular toxicity studies following intravitreal (ITV) administration of VEGF Trap included mild and transient increases in anterior segment and vitreous inflammation. Epithelial erosion/ulceration of the nasal turbinates accompanied with chronic-active inflammation was noted in the ocular toxicity studies. Partial recovery was observed. Similar lesions in the nasal cavity were noted in systemic toxicity studies in monkeys following repeated, IV administration at exposures 42 and 56 times higher those observed after ITV administration in humans based on C_{max} and AUC, respectively. We are not aware of any similar nasal findings with any other VEGF inhibitor. Based on this finding, the applicant specifically monitored for this finding in the clinical trials.

Systemic toxicity studies in monkeys identified toxicities mostly related to the pharmacology of VEGF Trap. The main target organs included the bone, kidney, adrenals, ovary and, as noted above, nasal cavity. Other microscopic findings included vascular alterations in the brain choroid plexus and digestive tract (duodenum, stomach, gallbladder, pancreas), vascular degeneration and fibrosis in several tissues including the heart, and hepatic portal inflammation and periportal necrosis. Findings in the bone, nasal cavities, digestive system, liver, and brain (choroid plexus) were still present at recovery. A NOAEL was not established but these systemic adverse effects occurred at systemic exposures well in excess of the exposure observed in humans.

VEGF Trap adversely affected the female and male reproductive systems. Absent or irregular menses associated with alterations in female reproductive hormone levels, decreases in ovarian and uterus weights, ovarian and uterine microscopic alterations, reduction in sperm motility, and sperm morphological abnormalities were observed at all dose levels. All changes were reversible. A NOAEL was not established but these systemic adverse effects occurred at systemic exposures over 1500 times higher than the exposure observed in humans. These findings are well known class effects.

As expected, given the role of VEGF in organogenesis, VEGF Trap was embryotoxic and teratogenic in rabbits. Dose-related increases in fetal resorptions, abortions, and numerous fetal (external, visceral and skeletal) malformations were observed. A developmental NOAEL was not identified but systemic exposures were at least 600 times higher than those in humans. Free VEGF Trap was detected in amniotic fluid samples in the dose range-finding study in rabbits.

CARCINOGENICITY:

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. On June 1, 2009, a Type C meeting (telecon) was held to discuss Regeneron's Pharmacology/Toxicology program for treatment of AMD (IND 12,462) (b) (4). The Division agreed that these studies were not required.

REPRODUCTIVE TOXICOLOGY:

The potential effects of VGF Trap in male and female fertility were evaluated as part of the 6-month IV toxicity study in monkeys (Study # VGFT-TX-05009).

Absent or irregular menses associated with reductions in ovarian hormones (progesterone, inhibin B, and likely, estradiol) and increases in FSH levels were observed at ≥ 3 mg/kg during the dosing phase. Ovary weight changes at doses ≥ 3 mg/kg were accompanied by compromised luteal development and reduction of maturing follicles. Following recovery, all VEGF Trap-treated females presented normal ovarian folliculogenesis and presence of medium to large size corpora lutea. In addition, uterine and vaginal atrophy were not seen, indicating complete reversibility. The high-dose females still showed decreased weight of the ovaries (23% absolute weight and 9% relative to body weight) compared to controls. However, the reduced magnitude of the change suggests recovery was ongoing.

There were no clear test article-related effects on male reproductive hormone levels (FSH, LH, and testosterone). Decreased sperm motility and increased sperm abnormalities were evident at all doses in the treatment phase but were fully reversible after the treatment-free phase. Decreases were also observed in the weight of the seminal vesicles but without a histopathological correlate.

Therefore, a NOAEL for fertility was not determined. Based on C_{max} and $AUC_{0\text{-}168hrs}$ for free VEGF Trap observed at the 3 mg/kg IV dose, the lowest dose at which the findings were observed, the exposure was 4902-fold and 1546-fold higher, respectively, than the exposure observed in humans (C_{max} and $AUC_{0\text{-}last}$ of 0.0193 μg/mL and 0.119 μg•day/mL, respectively) after an ITV dose of 2 mg/eye every 4 weeks.

5. Clinical Pharmacology/Biopharmaceutics

As presented in the Clinical Pharmacology Review:

Absorption/Distribution

Following intravitreal administration of 2 mg per eye of aflibercept ophthalmic solution (Study VGFT-OD-0702.PK) to patients with AMD, the mean plasma Cmax of free aflibercept was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL) and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeat doses intravitreally every 4 weeks.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6 L.

The aflibercept: VEGF complex plasma concentrations reach C_{max} in 14 to 28 days following a 2-mg intravitreal administration with a mean plasma C_{max} of approximately 0.186 mcg/mL (range from 0.100 to 0.286 mcg/mL).

Metabolism/Elimination
Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

The exploratory subgroup analyses in Phase 3 study VIEW 2 did not reveal any clinically relevant influence of the covariants including age, sex, BMI, renal function (determined as creatinine clearance), or geographic region (Europe *vs.* Japan) on the plasma concentrations of free aflibercept or aflibercept :VEGF complex.

6. Sterility Assurance

As presented in the Drug Substance Microbiology Review: Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective.

The formulated bulk drug substance process is described adequately for each drug product fill site. The material is released from the drug substance manufacturing site at (b) (4) (b) (4) Aflibercept for ophthalmic use is produced by (b) (4) The manufacturing process has adequate microbial controls. The applicant was asked to provide qualification data for the bioburden and endotoxin test methods used for testing (b) (4) along with summary data from 3 lots of each (b) (4) . The bioburden and endotoxin tests were shown to be suitable for their intended use.

For the drug product, aflibercept is presented as a sterile solution in vials closed with rubber stoppers and flip caps. (b) (4)

The drug product Product Quality Microbiology Review was completed August 3, 2011. The reviewer identified multiple deficiencies in the application which in their opinion precluded approval of aflibercept injection in this review cycle. The deficiencies identified by the Product Quality Reviewer are located in CDTL Review as well as the Product Quality Microbiology Review.

7. Clinical/Statistical - Efficacy

(b) (4)

Consistent with the previously approved products for this indication, the primary efficacy variable was the proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in ETDRS letter score compared to Baseline (i.e., prevention of moderate vision loss). The primary analysis demonstrated the non-inferiority (within 10%) of aflibercept to ranibizumab for each of the following: Aflibercept 2mg q4 weeks versus ranibizumab 0.5mg q4 weeks, Aflibercept 0.5mg q4 weeks versus ranibizumab 0.5mg q4 weeks, Aflibercept 2mg q8 weeks versus ranibizumab 0.5 mg q4 weeks. The subsequent test for superiority of aflibercept to ranibizumab failed to demonstrate superiority.

VIEW #1: Efficacy Analysis (PP Population with observed cases)

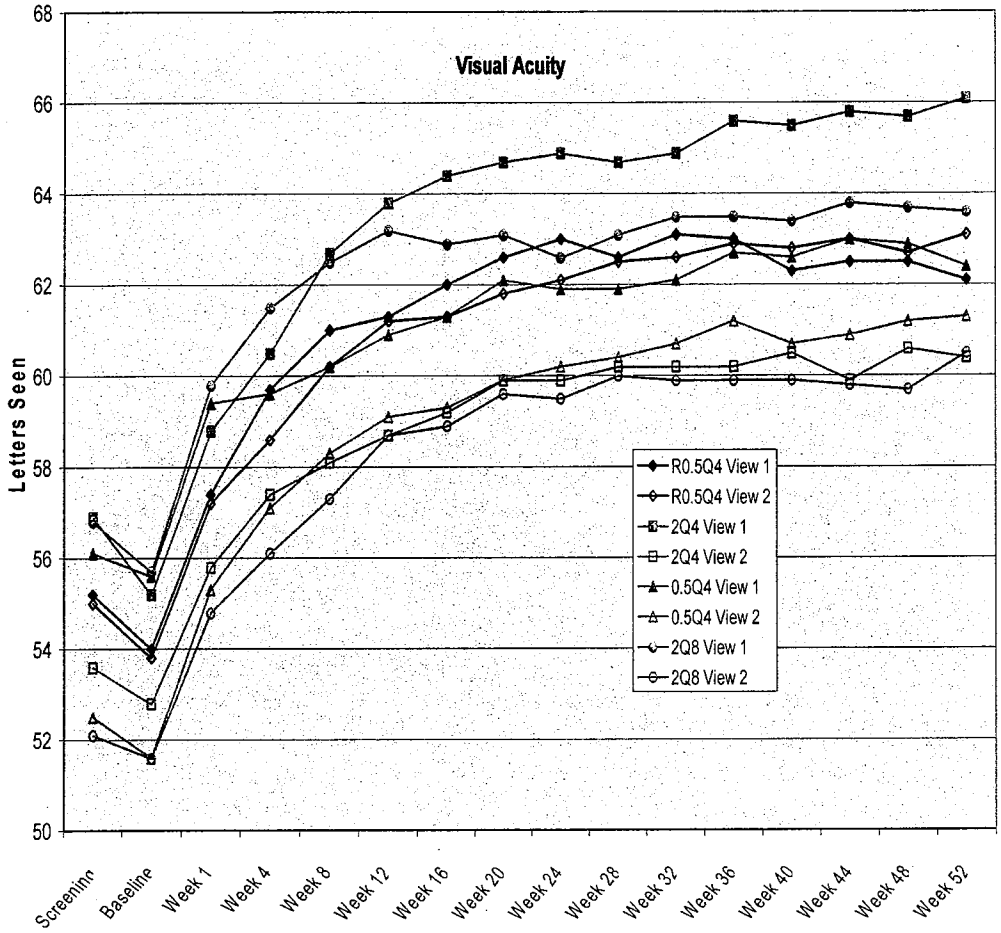
	R0.5Q4	**2Q4**	**0.5Q4**	**2Q8**
	N=269	**N=285**	**N=270**	**N=265**
Subjects With Maintained vision at Week 52	243/256	260/274	241/258	237/246
	(94.9%)	(94.9%)	(96.4%)	(96.3%)
Difference (%) (95.1% CI)		0.0	-1.5	-1.4
		(-3.7, 3.8)	(-5.0, 2.1)	(-5.0, 2.2)

VIEW #2: Efficacy Analysis (PP Population with observed cases)

	R0.5Q4	**2Q4**	**0.5Q4**	**2Q8**
	N=269	**N=274**	**N=268**	**N=270**
Subjects With Maintained vision at Week 52	246/261	251/263	248/257	253/264
	(94.3%)	(95.4%)	(96.5%)	(95.8%)
Difference (%) (95.1% CI)		-1.2	-2.3	-1.6
		(-4.99, 2.62)	(-5.87, 1.38)	(-5.31, 2.15)

As noted above, all 3 doses were non-inferior to ranibizumab in the proportion of subjects who maintained vision (lost less than 15 letters lost in the ETDRS letter score). None of the doses were superior to ranibizumab.

The findings are consistent among the different evaluable populations and among the subgroups defined by age (<65 years, ≥65 years to <75 years, ≥75 years), gender, race, ethnicity, baseline VA (better than 20/100 [≥50 letters]), between 20/100 and 20/200 (≥35 to <50 letters), worse than 20/200 (<35 letters), lesion size, lesion type, and country.



Additional Efficacy Issues/Analyses

Study VGFT-OD-0702 compared 2 different formulations of drug: vial and pre-filled syringe.

VGFT-OD-0702 was a single-masked (to the subject), randomized, multi-center 3 year clinical study. Subjects were eligible if they had neovascular AMD and completed dosing in VGFT-OD-0502, VGFT-OD-0508, or VGFT-OD-0603. Subjects were initially enrolled to receive VEGF Trap-Eye from a Vial. After 152 subjects had been enrolled, a PFS syringe was introduced as a result of Protocol Amendment 1. From that point, upon enrollment, subjects were randomly assigned in2:1 ratio to receive:

- 2 mg VEGF Trap-Eye PRN in a 50 µL injection volume from a PFS (Single-use, PFS glass syringes with Snap-off Tip Cap. A plastic plunger rod was attached to the rubber stopper inside the barrel of the syringe. After removing the syringe cap, a 30-gauge needle was attached for administration).

- 2 mg VEGF Trap-Eye PRN in a 50 µL injection volume from a Vial (Sealed, sterile 3 mL Vials of approximately 0.5 mL of VEGF Trap-Eye. The VEGF Trap-Eye was withdrawn into a 1 mL syringe using aseptic technique. A sterile 30-gauge needle was used for intravitreal injection).

VGFT-OD-0702: Mean ETDRS Letter Score (Full Analysis Set with LOCF) Cut Off Date 6/28/2010

	Vial N=45	PFS N=87
Baseline	60.2	62.4
Week 8	59.3	62.6
Week 16	60.6	61.7
Week 24	59.9	61.1
Week 32	59.6	60.6
Week 40	60.0	60.6
Week 48	59.1	60.6
Week 56	58.9	60.5
Week 64	58.2	58.8
Week 72	57.1	59.5
Week 80	57.6	59.7
Week 88	56.6	59.6
Week 96	56.8	58.1
Week 104	56.3	58.6
Week 112	56.1	58.6
Week 120	55.2	58.7
Week 128	55.2	58.4
Week 136	55.7	58.3
Week 144	55.6	58.3
Week 152	55.6	58.3
Week 156	55.6	58.3

Mean numbers of injections per subject were similar between the groups (5.8 and 6.2 in the Vial and PFS groups, respectively). The durations that subjects were in the study were similar. VA over time followed a similar trend in the 2 groups. The slow decrease in VA is consistent with PRN dosing.

Summary Efficacy Statement

Adequate and well controlled studies (VIEW #1, VIEW #2, and VGFT-OD-0702) support the efficacy of aflibercept injection for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD).

8. Safety

From the original Medical Officer Review: The main support for safety and efficacy for the AMD indication comes from the following trials: VIEW #1, VIEW #2, and VGFT-OD-0702. In these 3 trials there were a total of 2,614 patients.

Disposition of Subjects

VIEW 1&2: Disposition (All Randomized Subjects)

	R0.5Q4	2Q4	0.5Q4	2Q8
Randomized	609	617	615	616
Completed first year of study	560	574	551	560
Discontinuation from study with first year	49	43	64	56
Adverse event	6	9	13	13
Death	4	4	4	8
Withdrawal by subject	21	20	20	19
Protocol deviation	5	1	4	1
Lost to follow-up	5	3	6	6
Treatment failure	0	0	3	3
Other	8	6	14	6

Study VGFT-OD-0702: Disposition (All Enrolled Set)

	N=149
Subjects Prematurely Terminated From Study	28
Withdrawn Due to AE	4
Investigator Decision	2
Subject Request for Withdrawal	8
Lost to f/u	3
Death	7
Other	4

Listing of Deaths (Safety Analysis Set- View 1&2)

Subject Number	Treatment Group	Study Day	Number of Days After Last Dose	Cause
145-022	RQ4	19	19	Myocardial infarction
502-001	RQ4	223	83	Hepatic neoplasm
502-008	RQ4	259	35	Lung neoplasm
506-011	RQ4	259	77	CHF
507-019	RQ4	368	33	Aspiration pneumonia
160020002	RQ4	398	unknown	Esophageal CA
440030022	RQ4	118	3	Acute MI
142-027	2Q4	206	15	COPD
314-002	2Q4		54	Respiratory insufficiency
100220010	2Q4	90	35	CVA
600090017	2Q4	359	77	Pyrexia*
600130001	2Q4	251	58	Cardiopulmonary failure
218-008	0.5Q4	99	13	Cerebral hemorrhage
502-003	0.5Q4	80	53	Myocardial infarction
240090004	0.5Q4	unknown	unknown	unknown
760010013	0.5Q4	46	18	MI
114-018	2Q8	144	4	Hemorrhagic shock
146-016	2Q8	211	15	CVA

Subject Number	Treatment Group	Study Day	Number of Days After Last Dose	Cause
182-002	2Q8	313	33	Myocardial infarction
237-003	2Q8	171	31	Arteriosclerosis
284-002	2Q8	113	29	CHF
305-006	2Q8	150	31	Leukemia
309-009	2Q8	233	9	COPD
505-004	2Q8	257	56	CHF
430060004	2Q8	196	27	Lung CA
600040008	2Q8	60	4	Cardiac arrest

- *This patient had experienced a road traffic accident causing polytrauma a few weeks before that fatal pyrexia.*

Study VGFT-OD-0702: Listing of Deaths

Subject Number	Study Day (relative to first dose)	Number of Days After Last Dose	Cause
001-0112	902	43	Unknown at this time
015-1501	748	216	Stroke
018-1801	725	88	Lung CA
020-2007	946	159	Lung CA
027-2709	1006	670	Myocardial infarction
028-2806	603	295	Respiratory failure
044-4401	1175	106	Pulmonary edema
005-0504	1101	564	Lung CA

The deaths were not considered to be related to therapy.

Common Ocular Adverse Events in View 1&2

A treatment-emergent adverse event was defined as an event that was observed or reported after administration of study drug that was not present prior to study drug administration or an event that represented an exacerbation of a pre-existing event.

	R0.5Q4 N=595	2Q4 N=613	0.5Q4 N=601	2Q8 N=610
Number of subjects with at least 1 ocular TEAE in study eye	433	419	408	436
Conjunctival hemorrhage	167	133	157	161
Eye pain	53	66	49	43
IOP increased	41	38	27	30
Macular degeneration	39	43	40	40
Retinal hemorrhage	48	36	47	50
Visual acuity reduced	40	50	57	53
Vitreous detachment	33	44	32	34

The most common adverse reactions (≥5%) reported in patients receiving aflibercept injection were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, retinal hemorrhage, and increased intraocular pressure. Many of these events are associated with the disease being treated.

Drug- Specific Safety Explorations

IMMUNOGENICITY
For both VIEW #1 and VIEW #2 samples for ADA (anti-drug-antibody) were taken at Screening and subsequently on Weeks 12, 24, 36, and 52. All samples were drawn prior to injection of study drug.

VIEW 1&2: Number of Subjects with Anti-VEGF Trap Antibodies By Treatment Group (Safety Analysis Set)

	R0.5Q4 N=595	2Q4 N=613	0.5Q4 N=601	2Q8 N=610
Negative	567	576	567	600
Positive	23 (4%)	28 (5%)	27 (4%)	9 (1%)
Not drug induced	8	11	16	6
Transient	10	9	7	2
Persistent	5	8	4	2
Missing*	5	9	7	1

*Subjects with no sample collection of subjects with missing post-baseline sample.

These results show that the observed levels of immunogenicity were relatively low and similar between the different groups.

NASOMUCOSAL EXAMINATION (ENT SUB-STUDY)
A subset of 160 subjects in VIEW #2 was additionally examined by an ENT specialist, including nasal endoscopy (ENT sub-study). The purpose of the ENT sub-study was to better define potential nasomucosal side effects which were reported as histopathologic findings in a toxicology study (VGFT-TX-0511 or COV7369-112).

VIEW #2: ENT Sub-Study (Number with ENT Treatment Emergent AEs)

	R0.5Q4 N=37	2Q4 N=42	0.5Q4 N=37	2Q8 N=44
Nasal septum deviation	4	2	0	5
Nasal mucosal disorder	1	1	2	4
Rhinorrhea	0	1	2	4
Epistaxis	1	1	1	3
Nasal polyps	1	1	1	2
Nasal turbinate hypertrophy	0	0	1	2
Nasal dryness	0	0	0	1
Nasal mucosal discoloration	0	0	1	1
Nasal edema	0	0	0	1
Paranasal cyst	0	0	1	1
Rhinitis hypertrophy	1	0	0	0
Nasopharyngitis	5	2	4	8
Upper respiratory tract infection	1	1	1	4
Rhinitis	2	0	1	1
Viral rhinitis	0	0	1	1
Acute tonsillitis	1	0	0	0

The results of the ENT Sub-study in 160 patients at year 1 did not show an increased rate of nasal erosions or other ENT conditions associated with aflibercept compared to ranibizumab.

ARTERIAL THROMBOEMBOLIC EVENTS

VIEW 1&2: Number of Subjects with APTC Arterial Thromboembolic Events Through Year 1 (Safety Analysis Set)

	R0.5Q4 N=595	2Q4 N=613	0.5Q4 N=601	2Q8 N=610
Any APTC event	10 (1.7%)	6 (1.0%)	12 (2.0%)	14 (2.3%)
Non-fatal myocardial infarctions	6	3	6	6
Non-fatal strokes	2	2	3	3
Vascular deaths	2	1	3	5

Arterial thromboembolic events were a pre-specified AE of interest because of the association of thromboembolic events and VEGF inhibitors. There was no statistically significant difference between groups. There is no clear trend indentified for a particular dose or interval.

INTRAOCULAR PRESSURE

VIEW 1&2: Number of Subjects with an Absolute Value of IOP >= 35mmHg During the Study (Safety Analysis Set)

	R0.5Q4 N=595	2Q4 N=613	0.5Q4 N=601	2Q8 N=610
Any Visit	22	22	13	18

VIEW 1&2: Proportion of Subjects with >=10mmHg Increase in IOP from Baseline to Any Pre-Dose Measurement (Safety Analysis Set)

	R0.5Q4 N=595	2Q4 N=613	0.5Q4 N=601	2Q8 N=610
Pre-dose from baseline	19	8	14	14

Elevations in IOP following repeated dosing of VEGF-inhibitors has been reported in the literature.

There was no clear trend observed between groups in IOP elevation. The majority of IOP increases appeared to be post-dose measurements and secondary to the injection procedure itself.

Safety Summary Statement

The 12-Month Clinical Study Reports submitted within this BLA 125387 for VIEW #1, VIEW #2, and VGFT-OD-0702 support the safety of aflibercept injection in the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD).

The most common adverse reactions (≥5%) reported in patients receiving aflibercept injection were conjunctival hemorrhage, eye pain, cataract, retinal hemorrhage, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Observed levels of immunogenicity were relatively low and similar between the different groups, including the ranibizumab Q 4 week group in which subjects were not administered aflibercept. The results of the ENT Sub-study in 160 patients at year 1 did not show an increased rate of nasal erosions or other ENT conditions associated with aflibercept compared to ranibizumab.

There was no statistically significant difference between groups in arterial thromboembolic events. There was no clear trend indentified for a particular dose or interval.

The majority of IOP increases appeared to be post-dose measurements and secondary to the injection procedure itself.

The 2 mg Q 8 weeks dose is recommended for approval and inclusion in the labeling for the aflibercept product. Since the 2 mg Q 8 weeks dose has fewer injections than the other 2 studied doses (2 mg Q 4 weeks and 0.5 mg Q 4 weeks), approval is recommended for this specific dosage which has the theoretical benefit of less injection related risks (i.e. endophthalmitis).

In an eventual Postmarketing Requirement, the applicant should provide clinical information from a 1-year (minimum) clinical study to support that there are no adverse effects on the corneal endothelium in 100 eyes (minimum) following the intravitreal administration of aflibercept.

9. Advisory Committee Meeting

The Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration met on June 17, 2011. The committee unanimously (all 10 voting members) agreed that adequate safety and efficacy for aflibercept injection has been demonstrated for the treatment of neovascular age-related macular degeneration. The committee recommended 2mg every eight weeks (Q8) with an extra dose at month 2 (2mg monthly for 3 months then once every 2 months). The majority of the committee agreed that monitoring should be at the discretion of the physician and not be required.

10. Pediatrics

The population studied for this indication was predominantly in the 7th and 8th decades of life reflective of the population most affected by this disease. The demographics of the patients enrolled in the trial during the development program for this proposed indication are representative of the targeted population. The applicant requested a waiver of the pediatric study requirements (b) (4) for this original Biologics License Application. The waiver was requested because the disease under study (Neovascular (Wet) Age-Related Macular Degeneration (AMD) does not exist in children. The Pediatric Review Committee agreed with the Division to grant a full waiver for this product.

11. Other Relevant Regulatory Issues

CDRH CONSULTATION

In a consultation request dated May 27, 2011, the Product Quality reviewer requested that the Center for Devices and Radiological Health (CDRH). As noted in the Cross Disciple Team Leader memo, the CDRH review does not take into account the clinical testing previously conducted and submitted which addresses the requests for information in the consult response.

FINANCIAL DISCLOSURE

Regeneron has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There is no evidence to suggest that the results of the studies were impacted by any financial payments.

OSI

An Office of Scientific Investigations (OSI) audit was requested. The audit finding do not suggest any reason to question the data reliability.

12. Labeling

The labeling submitted by Regeneron on November 17, 2011, and found below and in the Cross-Discipline Team Leader Review is acceptable. The established name remains a source of disagreement within the review team. The Clinical Ophthalmology group has recommended that the established name be aflibercept injection. This name would include the dosage form in the name and be consistent with other ophthalmic products. Others have recommended that name not include the dosage form for consistency with most other biologic products. The most recently approved biologic ophthalmic product, Lucentis (ranubizamab injection) does include the dosage form in the name. It is my recommendation that the established/official/proper name of the product be aflibercept injection because the use a different name would treat this product differently than a similarly situated product, namely ranibizumab injection. Consistency with the product ranibizumab injection is relevant because it is also a biologic product for the treatment of age-related macular degeneration; ranibizumab injection was the direct comparator to EYLEA in the clinical trials which supported the approval of this BLA, and ranibizumab injection is listed in the draft package insert for EYLEA as Lucentis (ranibizumab injection).

Using the name aflibercept injection for the product would make the product consistent with other ophthalmologic products including the only other products approved for use in the treatment of age-related macular degeneration, Visudyne (vertiporfin for injection), Macugen (pegaptanib injection) and Lucentis (ranibizumab injection). While it has been noted that including the dosage form would not make it consistent with many other biologic products, the biologic products which do not include the dosage form in the name are not approved for use in the treatment of age-related macular degeneration. Based on a decision by the Office of Antimicrobial Products Director, the product will be approved with the name EYLEA (aflibercept).

13. Recommendations/Risk Benefit Assessment

BLA 125-387 for Eylea (aflibercept) is recommended for approval at this time.

Wiley A. Chambers, MD
Deputy Division Director
Division of Transplant and Ophthalmology Products

Cross-Discipline Team Leader Review

Date	August 12, 2011
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	125387
Applicant	Regeneron Pharmaceuticals, Inc.
Date of Submissions	February 18, 2011
PDUFA Goal Date	August 18, 2011
Proprietary Name / Established (USAN) names	Eylea (aflibercept injection)
Dosage forms / Strength	40 mg/mL solution for intravitreal injection
Proposed Indication(s)	treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD)
Recommended:	Not recommended for Approval

1. Introduction

AMD is a leading cause of blindness in developed countries. AMD is characterized as a progressive degenerative disease of the macula. There are two forms of AMD: neovascular and non-neovascular. The non-neovascular form of AMD is more common and leads to a slow deterioration of the macula with a gradual loss of vision over a period of years. The neovascular form of the disease is responsible for the majority of cases of severe vision loss and is due to proliferation of abnormal blood vessels behind the retina. These blood vessels leak blood and fluid into the retina, which results in visual abnormalities. The development of these abnormal blood vessels is due in part to the activity of VEGF (vascular endothelial growth factor), and its inhibition is expected to impact on the onset and/or severity of vision loss associated with the proliferation of abnormal blood vessels.

VEGF Trap (aflibercept injection) is a recombinant protein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to an IgG1 Fc. VEGF Trap is a specific antagonist that binds and inactivates circulating VEGF and PlGF (placental growth factor 1) in the blood stream and in the extravascular space. In comparison, pegaptanib (Macugen) is an inhibitor of the VEGF165 isomer and ranibizumab (Lucentis) and bevacizumab (Avastin) are inhibitors of all VEGF-A isomers.

Approved products for this proposed indication are:

NDA/BLA	Drug	Approval	Indication
NDA 21-119	Photodynamic therapy (PDT)/ Verteporfin	April 2000	Indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to AMD, pathologic myopia, or POHS.
NDA 21-756	Macugen (pegaptanib injection)	December 2004	Indicated for the treatment of neovascular (wet) age-related macular degeneration
BLA 125-156	Lucentis (ranibizumab injection)	June 2006	Indicated for the treatment of patients with neovascular (wet) age-related macular degeneration

In addition to the products listed above, focal laser therapy has been used to close abnormal leaking vessels secondary to AMD; the use of focal laser as initial therapy has declined greatly since the approval of the above drugs.

Throughout this review, Eylea (aflibercept injection) may be alternately referred to by some disciplines as VEGF Trap.

2. Background

IND 12,462 for VEGF Trap-Eye for the treatment of wet AMD was opened on June 15, 2005.

A No-Agreement letter was sent to Regeneron on March 5, 2007, regarding their January 18, 2007, Special Protocol Assessment (SPA) request for the Phase 3 Study VGFT-OD-0605. A second No-Agreement letter was sent to Regeneron on July 13, 2007, regarding their May 31, 2007, SPA amendment for the Phase 3 Study VGFT-OD-0605.

On June 1, 2009, a Type C meeting (telecon) was held to discuss Regeneron's Pharmacology/Toxicology program for treatment of AMD (IND 12,462 (b) (4) (b) (4)

(b) (4)

On September 8, 2010, a preBLA Clinical meeting was held to discuss clinical, clinical pharmacology, statistical, and regulatory issues concerning the upcoming BLA submission for treatment of AMD.

On September 27, 2010, a preBLA CMC meeting was held to discuss plans for Regeneron's submission of the BLA for treatment of AMD.

On June 17, 2011, the FDA Dermatologic and Ophthalmic Drug Advisory Committee reviewed BLA 125387. The committee unanimously agreed (all 10 voting members) that

adequate safety and efficacy for aflibercept injection had been demonstrated for the treatment of neovascular age-related macular degeneration.

3. Product Quality

From the original Product Quality Review:

DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name:	Eylea
Non-proprietary/USAN:	Aflibercept injection
Code name:	VEGF Trap-EYE, BAY 86-5321
Common name:	Vascular endothelial growth factor receptor type VEGFR (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer
Drug Review Status:	Priority
Chemical Type:	recombinant fusion protein of human VEGFR1 Ig domain 2, human VEGFR2 Ig domain 3, and human IgG1 Fc

PHARMACOLOGIC CATEGORY: Therapeutic recombinant fusion protein of human VEGFR1 Ig domain 2, human VEGFR2 Ig domain 3, and human IgG1 Fc

DOSAGE FORM: intravitreal injection (vial) (b) (4)

STRENGTH/POTENCY:

a) The concentration of Eylea (aflibercept injection) Drug Product is 40 mg/ml.
b) Potency is defined as IC_{50} of the sample relative to IC_{50} of the reference standard in a proprietary VEGF-stimulated reporter gene assay.
c) Proposed potency specification is (b) (4) of reference standard.
d) Proposed dating period for vialed drug product is 24 months when stored at 2-8°C.
e) 11.12 mg of aflibercept is filled into (b) (4) glass vials or (b) (4) glass vials for a 2 mg dose.
f) (b) (4)

ROUTE OF ADMINISTRATION: Intravitreal Injection

Aflibercept is a dimeric IgG1 fusion protein. The Fc portion of human IgG1 is fused to human vascular endothelial growth factor receptor (VEGFR)-derived peptide domains. VEGFR2 extracellular Ig domain 3 is fused to the Fc region, and VEGFR1 extracellular Ig domain 2 is fused to the VEGFR2 domain. (b) (4)

(b) (4)

(b) (4) The theoretical (unglycosylated) molecular weight is 96.9 kD, and the experimental molecular weight is 115 kD. The isoelectric point is 5.8-8.3.

Table 2: Physicochemical and Biochemical Properties

Characteristic	Data
Description	Aflibercept is a recombinant homodimeric glycoprotein with a molecular weight of approximately 115,000 Daltons.
Quaternary structure	Covalent (disulfide linked) dimer

(b) (4)

DRUG SUBSTANCE:

The specifications for the DS intermediate are not in the following table.

For detailed discussion of the DS intermediate, see the original Product Quality review, Section 3.2.S.2.4.

Table 1: Release Tests and Acceptance Criteria for Aflibercept Drug Substance

TEST	ANALYTICAL METHOD	ACCEPTANCE CRITERION
Appearance a. Turbidity b. Visible assessment of particulates	Visual inspection Ph. Eur. 2.2.1, Ph. Eur. 2.9.20	a. Not greater than reference standard III b. Essentially free from visble particulates
Color	Ph. Eur. 2.2.2	Colorless to reference standard BY5
pH	USP <791>, Ph. Eur. 2.2.3	5.9 – 6.5
Identity by N-terminal Analysis	Edman degradation chemistry/ HPLC	SDTGRPFVEMYSEIP
Identity by Western Blot (αR2)	Immunoblotting	Conforms to reference standard
Total Protein Content (A_{280})	UV Spectrophotometry	43 – 72 mg/mL
Process-Related Impurities		
(b) (4)		
	(b) (4)	(b) (4)
(b) (4)		(b) (4)
Potency by Cell-based Bioassay	Cell-based assay	(b) (4) of Reference IC_{50}
Purity by SDS-PAGE		
Reduced – Coomassie stain	Slab gel electrophoresis	Aflibercept main band (b) (4) total band area
Non-Reduced – Coomassie stain a. % main band b. % non-reduced band 1 (NR1)	Slab-gel electrophoresis	a. Aflibercept main band (b) (4) total band area b. (b) (4)

DRUG PRODUCT:

(b) (4)

REGULATORY SPECIFICATIONS:

Table 1: 40 mg/mL Filled Drug Product Release Specification

Filled Unlabeled Container Test	Analytical Method	Acceptance Criterion
Appearance	Ph.Eur. 2.2.1, Ph.Eur. 2.9.20	a. Not greater than turbidity standard III b. Essentially free form visible particulates
Color	Ph. Eur. 2.2.2	Not greater than reference standard BY5
pH	USP <791>, Ph. Eur. 2.2.3	5.9 – 6.5
Identity by Western Blot (αR2)	Immunoblotting	Conforms to reference standard
Total Protein Content (A_{280})	UV Spectrophotometry	(b) (4) mg/mL
Potency by Cell-based Bioassay	Cell-based assay	(b) (4)
Purity by SDS-PAGE		
Reduced, Coomassie	Slab gel electrophoresis	Aflibercept main band (b) (4) total band area
Non-Reduced, Coomassie a. % main band b. % non-reduced band 1 (NR1)	Slab-gel electrophoresis	a. Aflibercept main band (b) (4) total band area (b) (4)
Purity by Size Exclusion HPLC a. % main peak b. % aggregate	Size exclusion HPLC/UV	a. Aflibercept main peak (b) (4) total peak area b. (b) (4) aggregate
Isoelectric Focusing a. Profile b. Total area of bands 3 – 9	Slab gel electrophoresis	a. Principal bands (b) (4) of test article correspond in position to principal bands (b) (4) of reference standard. b. Total area of bands (b) (4) (b) (4)
Isoaspartate Assay	Enzyme-linked detection of isoaspartate with reversed phase HPLC/UV	≤ 0.15 mol isoaspartate/mol aflibercept
Endotoxin content	USP <85>, Ph. Eur. 2.6.14 Limulus Amebocyte Lysate Kinetic Turbidimetric Assay	≤ 0.4 EU/mL
Particulate Matter	USP <789>, Ph. Eur. 2.9.19	(b) (4)
Sterility	USP <71>, Ph. Eur. 2.6.1	Meets USP, EP requirements
Volume in Container	USP <1> Ph. Eur. 2.9.17	(b) (4) minimum withdrawable content

The difference between filled Drug Product and finished Drug Product is labeling and packaging (Table 1 above versus Table 2 and Table 1 which follow).

Table 2: 40 mg/mL Finished Drug Product Release Specification

Finished Container Test	Analytical Method	Acceptance Criterion
Appearance	Ph.Eur. 2.2.1, Ph.Eur. 2.9.20	a. Not greater than turbidity standard III b. Essentially free form visible particulates
Color	Ph. Eur. 2.2.2	Not greater than reference standard BY5
Identity by Western Blot (αR2)	Immunoblotting	Conforms to reference standard.
Total Protein Content (A_{280})	UV Spectrophotometry	(b) (4) mg/mL
Labeling	Visual inspection	Labeling matches label masters

Table 1: (b) (4)

(b) (4)

Note: A final review of specifications can only be performed after all information requested has been submitted to the BLA. Therefore the specifications in the table(s) above are not final specifications agreed upon by the Agency and the applicant.

CONTAINER CLOSURE

From the draft package insert:

(b) (4)

Per the original Product Quality review, additional information should be submitted to the container closure sections of the BLA to more precisely identify the container closure systems used for each presentation. As of the date of this review, that additional information is pending.

INSPECTIONS

A pre-approval inspection (PAI) for aflibercept drug substance production at the Regeneron Rensselaer facility was conducted from May 16 to May 20, 2011. (b) (4) for manufacture of drug substance intermediate, drug substance, and formulated bulk and for QC testing. A form 483 was issued at the end of this inspection. Observations made during the inspection pertain to inadequate microbial control strategy for (b) (4) manufacture of aflibercept drug substance and QA documents that do not assure appropriate production record review and release of commercial material. This inspection was initially classified VAI; however, final classification is pending finalization of the review by CDER OC.

DEFICIENCIES

The Product Quality Reviewer has identified multiple deficiencies in the application which preclude approval of aflibercept injection in this review cycle. Some of these deficiencies have been previously transmitted to the applicant for a response; some of the deficiencies have not been previously transmitted to the applicant. Submissions to the BLA dated 7/1/11, 7/6/11, and 7/8/11 were not reviewed this cycle.

Because of their length, the deficiencies identified by the Product Quality Reviewer are located in **Appendix 1** of this CDTL Review. These include the deficiencies identified in the (b) (4) (b) (4)

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review:

VEGF Trap is a recombinant protein that is composed of two domains of the human VEGF cell surface receptors (VEGF R1 and VEGF R2) fused to the Fc region of human IgG. This recombinant molecule binds with high affinity to VEGF-A (K_D=0.36-0.76 pM) along with the related Placental Growth Factor (PlGF; K_D=29-392 pM). VEGF Trap has demonstrated anti-angiogenic activity in several preclinical animal models. In this BLA, this molecule is intended for the treatment of neovascular (wet) age-related macular degeneration (AMD) by intravitreal (ITV) injection of a 2 mg dose once every 2 months, following 3 initial 2 mg monthly injections.

The monkey was selected as the relevant species. Findings observed in ocular toxicity studies following ITV administration of VEGF Trap included mild and transient increases in anterior segment and vitreous cellularity (interpreted as a mild inflammation) that was not associated with other ocular abnormalities. These findings occurred at doses 0.5 times the intended clinical dose when correcting for vitreous volume (i.e., assuming a vitreous volume of 2 mL in monkeys and 4 mL in humans). However, the mild and transient nature of the finding does not represent a major clinical concern.

Epithelial erosion/ulceration of the nasal turbinates accompanied with chronic-active inflammation was noted in the ocular toxicity studies following ITV administration of VEGF Trap. Partial recovery was observed. Similar, albeit more severe lesions in the nasal cavity were noted in systemic toxicity studies in monkeys following repeated, IV administration. These findings occurred at exposures 42 and 56 times higher those observed after ITV administration in humans based on C_{max} and AUC, respectively. The reviewer is not aware of the observation of similar nasal findings with any other approved VEGF inhibitor following ITV injection. The applicant monitored for this finding in a subset of patients in the clinical trials.

Systemic toxicity studies in monkeys identified toxicities mostly related to the pharmacology of VEGF Trap. The main target organs included the bone, kidney, adrenals, ovary and, as noted above, nasal cavity. Other microscopic findings included vascular alterations in the brain choroid plexus and digestive tract (duodenum, stomach, gallbladder, pancreas), vascular degeneration and fibrosis in several tissues including the heart, and hepatic portal inflammation and periportal necrosis. Findings in the bone, nasal cavities, digestive system, liver, and brain (choroid plexus) were still present at recovery. A NOAEL was not established but these systemic adverse effects occurred at systemic exposures well in excess of the exposure observed in humans.

VEGF Trap adversely affected the female and male reproductive systems. Absent or irregular menses associated with alterations in female reproductive hormone levels, decreases in ovarian and uterus weights, ovarian and uterine microscopic alterations, reduction in sperm motility, and sperm morphological abnormalities were observed at all dose levels. All changes were reversible. A NOAEL was not established but these systemic adverse effects occurred at systemic exposures over 1500 times higher than the exposure observed in humans. These findings are well known class effects.

As expected, given the role of VEGF in organogenesis, VEGF Trap was embryotoxic and teratogenic in rabbits. Dose-related increases in fetal resorptions, abortions, and numerous fetal (external, visceral and skeletal) malformations were observed. A developmental NOAEL was not identified but systemic exposures were at least 600 times higher than those in humans. Free VEGF Trap was detected in amniotic fluid samples in the dose range-finding study in rabbits.

VEGF inhibitors, as a class, are known to increase blood pressure. Elevations in blood pressure were primarily observed in rats and mice after systemic administration. No effects were noted after ITV administration in monkeys. The blood pressure remained elevated above pre-treatment baseline values until circulating VEGF Trap levels fell below ~ 1 μg/mL in both rats and mice. The mean C_{max} observed in humans is ~50 times lower than the identified threshold in rodents. The applicant monitored for changes in blood pressure in the clinical trials.

CARCINOGENICITY:

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. On June 1, 2009, a Type C meeting (telecon) was held to discuss Regeneron's Pharmacology/Toxicology program for treatment of AMD (IND 12,462) (b) (4) (b) (4) The Division agreed that these studies were not required.

REPRODUCTIVE TOXICOLOGY:

The potential effects of VGF Trap in male and female fertility were evaluated as part of the 6-month IV toxicity study in monkeys (Study # VGFT-TX-05009).

Absent or irregular menses associated with reductions in ovarian hormones (progesterone, inhibin B, and likely, estradiol) and increases in FSH levels were observed at ≥ 3 mg/kg during

the dosing phase. Ovary weight changes at doses ≥ 3 mg/kg were accompanied by compromised luteal development and reduction of maturing follicles. Following recovery, all VEGF Trap-treated females presented normal ovarian folliculogenesis and presence of medium to large size corpora lutea. In addition, uterine and vaginal atrophy were not seen, indicating complete reversibility. The high-dose females still showed decreased weight of the ovaries (23% absolute weight and 9% relative to body weight) compared to controls. However, the reduced magnitude of the change suggests recovery was ongoing.

There were no clear test article-related effects on male reproductive hormone levels (FSH, LH, and testosterone). Decreased sperm motility and increased sperm abnormalities were evident at all doses in the treatment phase but were fully reversible after the treatment-free phase. Decreases were also observed in the weight of the seminal vesicles but without a histopathological correlate.

Therefore, a NOAEL for fertility was not determined. Based on C_{max} and $AUC_{0\text{-}168hrs}$ for free VEGF Trap observed at the 3 mg/kg IV dose, the lowest dose at which the findings were observed, the exposure was 4902-fold and 1546-fold higher, respectively, than the exposure observed in humans (C_{max} and $AUC_{0\text{-}last}$ of 0.0193 μg/mL and 0.119 μg•day/mL, respectively) after an ITV dose of 2 mg/eye every 4 weeks.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review:

In patients with neovascular AMD, following intravitreal administration of aflibercept injection, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept:VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept:VEGF complex).

Absorption/Distribution
Following intravitreal administration of 2 mg per eye of aflibercept injection (Study VGFT-OD-0702.PK) to patients with AMD, the mean plasma Cmax of free aflibercept was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL) and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeat doses intravitreally every 4 weeks.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6 L.

The aflibercept: VEGF complex plasma concentrations reach C_{max} in 14 to 28 days following a 2-mg intravitreal administration with a mean plasma C_{max} of approximately 0.186 mcg/mL (range from 0.100 to 0.286 mcg/mL).

Metabolism/Elimination
Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

The exploratory subgroup analyses in Phase 3 study VIEW 2 did not reveal any clinically relevant influence of the covariants including age, sex, BMI, renal function (determined as creatinine clearance), or geographic region (Europe *vs*. Japan) on the plasma concentrations of free aflibercept or aflibercept :VEGF complex.

6. Sterility Assurance

I. DRUG SUBSTANCE

From the original drug substance Product Quality Microbiology Review:

Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective.

VEGF Trap (aflibercept) is a recombinant protein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to the Fc portion of an IgG1 molecule. Manufacture of VEGF Trap involves culture of recombinant Chinese hamster ovary (CHO) cells and subsequent purification [redacted] (b) (4) VEGF Trap drug substance [redacted] (b) (4) [redacted] (b) (4) [redacted]

FORMULATED BULK MANUFACTURING PROCESS
The formulated bulk drug substance process is described adequately under the [BLA] 3.2 P section for each drug product fill site. [redacted] (b) (4) [redacted]

CONTROLS OF CRITICAL STEPS AND INTERMEDIATES
Aflibercept DS for ophthalmic use via intravitreal administration is produced [redacted] (b) (4) (b) (4)

CONTROL OF DRUG SUBSTANCE
The bioburden and endotoxin drug substance release specification are shown below:

TEST	ANALYTICAL METHOD	ACCEPTANCE CRITERION
Bioburden	Membrane filtration technique USP<61> Ph. Eur. 2.6.12	≤ 10 CFU/10 mL
Endotoxin Content	USP <85>, Ph. Eur. 2.6.14 Limulus Amebocyte Lysate Kinetic Turbidimetric Assay	≤ 0.4 EU/mL

The [Bioburden] test was shown to be suitable for its intended use.

The endotoxin test was shown to be suitable for its intended use.

CONTAINER CLOSURE SYSTEM
The results of the container closure integrity testing indicated that the containers are adequately sealed. The drug substance is [redacted] (b) (4)

II. DRUG PRODUCT

From BLA Section 5.2:

MICROBIOLOGICAL ATTRIBUTES – DRUG PRODUCT IN [redacted] (b) (4) VIALS
The VEGF Trap-Eye drug product is presented as a sterile solution [redacted] (b) (4) [redacted] (b) (4) in vials closed with rubber stoppers and flip caps. [redacted] (b) (4)

CONTAINER CLOSURE INTEGRITY TESTING - [redacted] (b) (4)
The container closure system was selected on the basis of its ability to protect the quality of the drug product over its shelf life. The integrity of the primary container closure system was challenged as part of process validation by dye leak testing. The dye leak test for container

closure integrity is used to assess the effectiveness of the individual container closure components to prevent any leakage. To perform the dye leak test, (b) (4) (b) (4) are submerged in a pressure vessel filled with a methylene blue solution. The closed vessel is subsequently manipulated through different pressure cycles. The test units are cleaned and visually inspected. Negative control (b) (4) that were not subjected to testing are also cleaned and visually inspected. Any visual incursion of blue dye into the (b) (4) constitutes a failure. This dye test was performed using (b) (4) units from all validation batches.

A microbiological container closure integrity test was performed utilizing (b) (4) the container closure specific media fill. Before the test execution the test units were pre-incubated (b) (4) After incubation, the test units were visually inspected as the integrity test was performed only with sterile test units. A growth promotion test was performed on the test units along with positive and negative control units. The test units were placed in a pressure vessel with an inoculated bacterial suspension solution. The vessel was closed and then negative, atmospheric, and over-pressure situations were applied.

CONTAINER CLOSURE INTEGRITY TESTING - DRUG PRODUCT IN VIALS

(b) (4) the pre-incubated time was 9 days (b) (4) regarding the microbiological container closure integrity test.

The drug product Product Quality Microbiology Review was completed August 3, 2011. From that review:

The scope of this review is product quality microbiology information provided for drug product vials manufactured at (b) (4), drug product vials manufactured at (b) (4) (b) (4)

The microbial test specifications for DP in vials (10 mg/ml and 40 mg/ml) (b) (4) with endotoxin ≤ 0.4 EU/ml.

(b) (4)

The drug product Product Quality Microbiology Reviewer has identified multiple deficiencies in the application which preclude approval of aflibercept injection in this review cycle.

Because of their length, the deficiencies identified by the Product Quality Reviewer are located in **Appendix 2** of this CDTL Review.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review:

(b) (4)

Analysis of Primary Endpoint(s) – Maintained Vision at Week 52

The primary efficacy variable was the proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in ETDRS letter score compared to Baseline (i.e. prevention of moderate vision loss).

The primary analysis is an evaluation of the non-inferiority of VEGF Trap-Eye to ranibizumab and includes the following conditional sequence of calculations of the confidence intervals for the difference between treatments in proportion of subjects maintaining vision at Week 52:

Comparison 1: VEGF Trap-Eye 2mg q4 weeks versus ranibizumab
Comparison 2: VEGF Trap-Eye 0.5mg q4 weeks versus ranibizumab
Comparison 3: VEGF Trap-Eye 2mg q8 weeks versus ranibizumab

The non-inferiority margin in individual VIEW 1 and VIEW 2 studies was 10%. The primary analysis was a conditional sequence (a priori ordered hypotheses) of statistical evaluation of non-inferiority of VEGF Trap-Eye to 0.5 mg ranibizumab. VEGF Trap-Eye was to be considered non-inferior to ranibizumab if the confidence interval of the difference lay entirely below 10%, where a positive difference favors ranibizumab. These analyses were based on the PP at Week 52. Once the non-inferiority was demonstrated, the superiority of VEGF Trap-Eye to ranibizumab was examined.

Patient Populations for VIEW #1 and VIEW #2:

Safety analysis set (SAF): All subjects who received any study drug.

Full analysis set (FAS): All randomized subjects who received any study drug and had a Baseline and at least one post-Baseline BCVA assessment.

Per protocol set (PP): All subjects in the FAS who received at least 9 injections of study drug or sham and attended at least 9 scheduled visits during the first year, except for those who were excluded because of major protocol violations. A major protocol violation is one that may affect the interpretation of study results (ie. missing two consecutive injections before administration of the 9th injection). Sham injections were counted as doses administered for the purpose of defining the PP. The PP also included subjects without major protocol deviations who discontinued due to treatment

failure at anytime during the first 52 weeks of the study. A treatment failure is a subject who had a decrease from Baseline in BCVA of at least 15 letters at two consecutive assessments, 4 weeks apart, during the first 52 weeks of the study.

VIEW #1: Primary Efficacy Analysis (FAS Population with LOCF)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=301	2Q8 N=301
Subjects With 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)

VIEW #1: Primary Efficacy Analysis (PP Population with observed cases)

	R0.5Q4 N=269	2Q4 N=285	0.5Q4 N=270	2Q8 N=265
Subjects With Maintained vision at Week 52	243/256 (94.9%)	260/274 (94.9%)	241/258 (96.4%)	237/246 (96.3%)
Difference (%) (95.1% CI)		0.0 (-3.7, 3.8)	-1.5 (-5.0, 2.1)	-1.4 (-5.0, 2.2)

VIEW #2: Primary Efficacy Analysis (FAS Population with LOCF)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=296	2Q8 N=306
Subjects With Maintained vision at Week 52	276 (94.9%)	292 (94.5%)	282 (95.3%)	292 (95.4%)
Difference (%) (95.1% CI)		0.4 (-3.3, 4.0)	-0.4 (-4.0, 3.1)	-0.6 (-4.1, 2.9)

VIEW #2: Primary Efficacy Analysis (PP Population with observed cases)

	R0.5Q4 N=269	2Q4 N=274	0.5Q4 N=268	2Q8 N=270
Subjects With Maintained vision at Week 52	246/261 (94.3%)	251/263 (95.4%)	248/257 (96.5%)	253/264 (95.8%)
Difference (%) (95.1% CI)		-1.2 (-4.99, 2.62)	-2.3 (-5.87, 1.38)	-1.6 (-5.31, 2.15)

In Study VIEW #2, the applicant did not adjust the CI to 95.1% for the interim safety look. The Agency did re-adjust the analysis to include a statistical adjustment as shown in the above tables.

Both studies met their primary endpoint. When compared to ranibizumab, all 3 doses of VEGF Trap-Eye were non-inferior when comparing the proportion of subjects who maintained vision (lost less than 15 letters lost in the ETDRS letter score). However, none of the doses were superior to ranibizumab.

From the original Statistical Review:

Subgroup analyses were performed for the following visual acuity efficacy variables:

- Proportion of subjects who maintained vision (<15 letters lost) (PPS and FAS),
- Change from baseline in BCVA at week 52 (FAS),

- Proportion of subjects who gained at least 15 letters of vision at week 52 (FAS).

The subgroups were defined by age (<65 years, ≥65 years to <75 years, ≥75 years), gender, race (white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander; OR: white or non-white), ethnicity, baseline VA (better than 20/100 [≥50 letters]), between 20/100 and 20/200 (≥35 to <50 letters), worse than 20/200 (<35 letters), lesion size (>10.16 mm^2 to ≤10.16 mm^2, equivalent to 4 DAs [2.54 mm^2 = 1 DA]), and lesion type (predominantly classic, minimally classic, and occult), and country in study VIEW 2.

The results of the subgroup analyses were overall consistent with those in the total population.

Analysis of Secondary Endpoints(s)

If all three VEGF Trap-Eye groups were shown to be non-inferior to ranibizumab on the primary endpoint, additional comparisons of VEGF Trap-Eye groups to ranibizumab were made with respect to secondary endpoints. The secondary efficacy analysis was conducted in the FAS population and was to test for superiority of VEGF Trap-Eye over ranibizumab. A conditional sequence of statistical hypotheses (a-priori ordered hypotheses) was to control for multiplicity for secondary endpoint analyses. The following sequence of analyses was performed:

1. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to subjects' mean change in BCVA as measured by ETDRS letter score from Baseline to Week 52.
2. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to the proportions of subjects who gained 15 or more letters of vision from Baseline to Week 52.
3. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to subjects' mean change in total NEI-VFQ-25 score from Baseline to Week 52.
4. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to subjects' mean change in BCVA as measured by ETDRS letter score from Baseline to Week 52.
5. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to the proportions of subjects who gained 15 or more letters of vision from Baseline to Week 52.
6. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to subjects' mean change in total NEI-VFQ-25 score from Baseline to Week 52.
7. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to subjects' mean change in BCVA as measured by ETDRS letter score from Baseline to Week 52.
8. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to the proportions of subjects who gained 15 or more letters of vision from Baseline to Week 52.
9. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to subjects' mean change in total NEI-VFQ-25 score from Baseline to Week 52.
10. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to subjects' mean change in CNV area from Baseline to Week 52.
11. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to subjects' mean change in CNV area from Baseline to Week 52.
12. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to subjects' mean change in CNV area from Baseline to Week 52.

Note: For both VIEW #1 and VIEW #2 none of the aflibercept doses were superior to ranibizumab. Thus, the conditional sequence of statistical hypothesis testing for superiority of VEGF Trap- Eye in a confirmatory manner had to stop after the first step. Therefore, all subsequent statistical tests no longer serve any confirmatory statistical hypothesis testing and only give descriptive indications for potential treatment differences.

VIEW #1: Mean Change from Baseline to Week 52 in ETDRS Letter Score in the Study Eye (Full Analysis Set with LOCF)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=301**	**2Q8 N=301**
Baseline				
Mean ETDRS letter score(sd)	54.0 (13.4)	55.2 (13.2)	55.6 (13.1)	55.7 (12.8)
Week 52				
Mean ETDRS letter score (sd)	62.1 (17.7)	66.1 (16.2)	62.4 (16.5)	63.6 (16.9)
Mean change from baseline at Week 52 (sd)	8.1 (15.3)	10.9 (13.8)	6.9 (13.4)	7.9 (15.0)

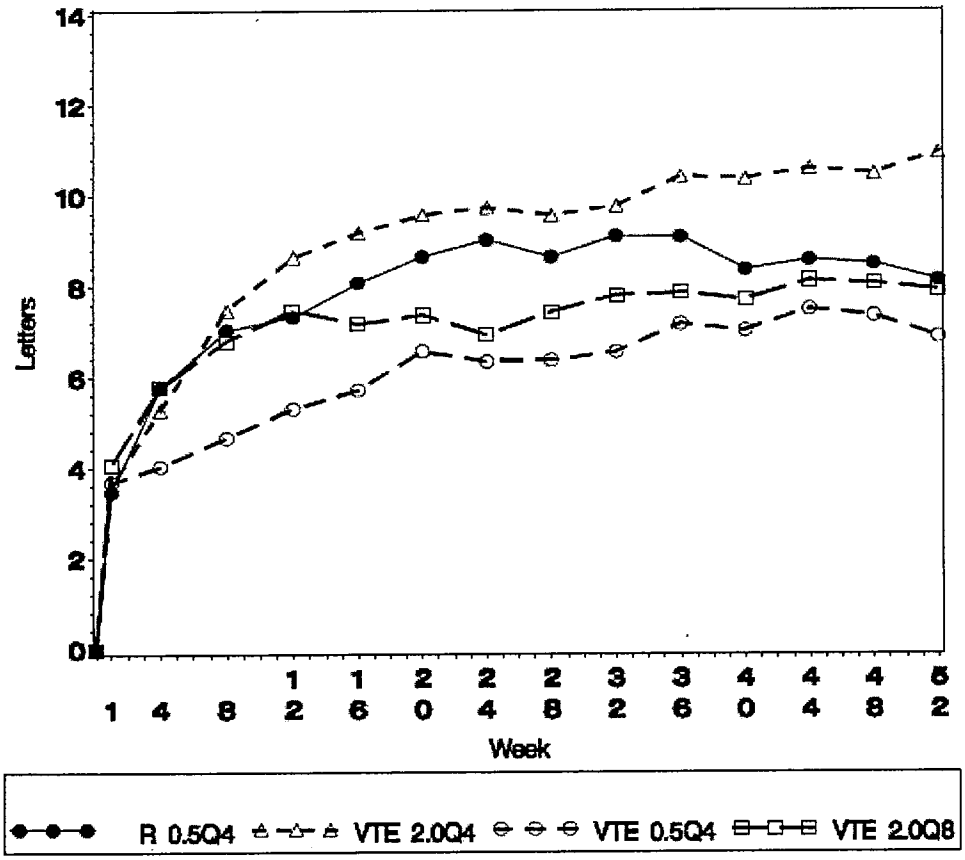
VIEW #1: Mean ETDRS Letter Score (Full analysis Set with LOCF)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=301**	**2Q8 N=301**
Screening	55.2	56.9	56.1	56.8
Baseline	54.0	55.2	55.6	55.7
Week 1	57.4	58.8	59.4	59.8
Week 4	59.7	60.5	59.6	61.5
Week 8	61.0	62.7	60.2	62.5
Week 12	61.3	63.8	60.9	63.2
Week 16	62.0	64.4	61.3	62.9
Week 20	62.6	64.7	62.1	63.1
Week 24	63.0	64.9	61.9	62.6
Week 28	62.6	64.7	61.9	63.1
Week 32	63.1	64.9	62.1	63.5
Week 36	63.0	65.6	62.7	63.5
Week 40	62.3	65.5	62.6	63.4
Week 44	62.5	65.8	63.0	63.8
Week 48	62.5	65.7	62.9	63.7
Week 52	62.1	66.1	62.4	63.6

VIEW #1: Mean Change in ETDRS Letter Score from Baseline (Full analysis Set with LOCF)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=301	2Q8 N=301
Week 1	3.5	3.6	3.7	4.1
Week 4	5.8	5.3	4.0	5.8
Week 8	7.0	7.5	4.7	6.8
Week 12	7.3	8.7	5.3	7.5
Week 16	8.1	9.2	5.7	7.2
Week 20	8.7	9.6	6.6	7.4
Week 24	9.0	9.7	6.3	6.9
Week 28	8.7	9.6	6.4	7.4
Week 32	9.1	9.8	6.6	7.8
Week 36	9.1	10.4	7.2	7.9
Week 40	8.4	10.4	7.0	7.7
Week 44	8.6	10.6	7.5	8.1
Week 48	8.5	10.5	7.4	8.1
Week 52	8.1	10.9	6.9	7.9

VIEW #1: Mean Change from Baseline in Visual Acuity through Week 52 by Treatment Group (Full Analysis Set with LOCF)



VIEW #2: Mean Change from Baseline to Week 52 in ETDRS Letter Score in the Study Eye (Full Analysis Set with LOCF)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=296**	**2Q8 N=306**
Baseline				
Mean ETDRS letter score (sd)	53.8 (13.5)	52.8 (13.9)	51.6 (14.2)	51.6 (13.9)
Week 52				
Mean ETDRS letter score (sd)	63.1 (16.6)	60.4 (18.3)	61.3 (17.8)	60.5 (17.5)
Mean change from baseline at Week 52 (sd)	9.4 (13.5)	7.6 (12.6)	9.7 (14.1)	8.9 (14.4)

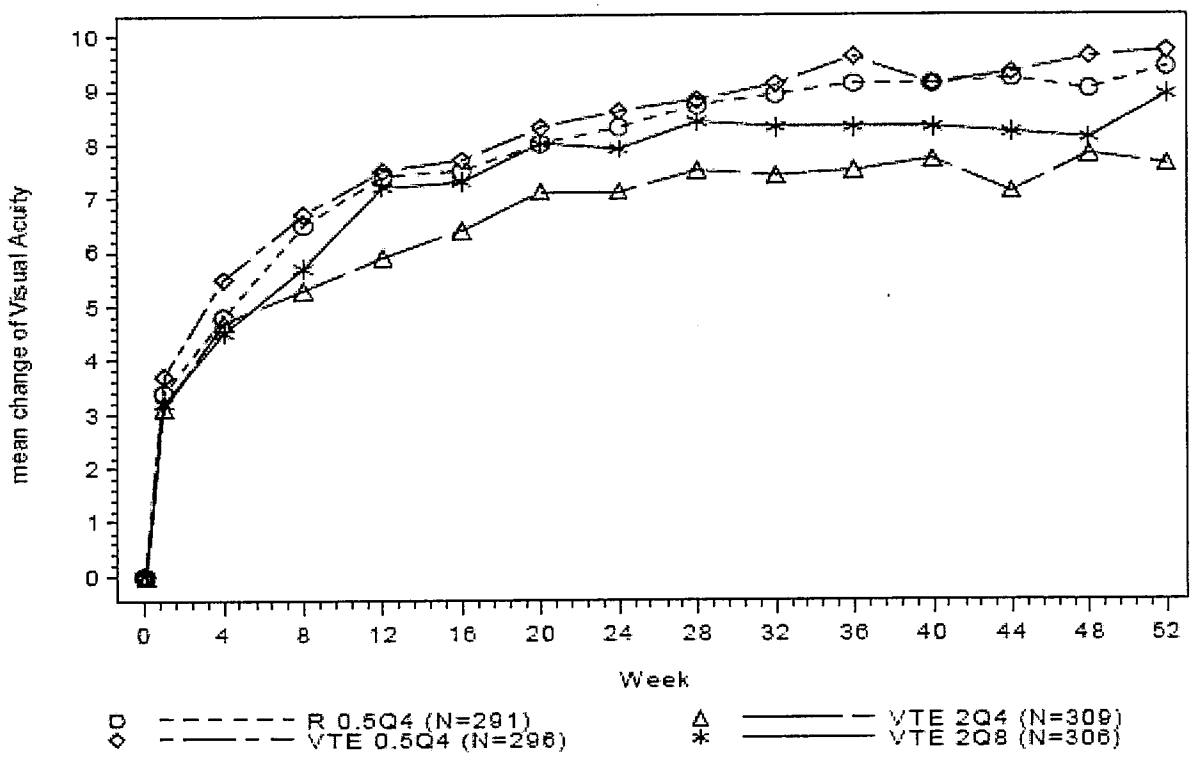
VIEW #2: Mean ETDRS Letter Score (Full analysis Set with LOCF)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=296**	**2Q8 N=306**
Screening	55.0	53.6	52.5	52.1
Baseline	53.8	52.8	51.6	51.6
Week 1	57.2	55.8	55.3	54.8
Week 4	58.6	57.4	57.1	56.1
Week 8	60.2	58.1	58.3	57.3
Week 12	61.2	58.7	59.1	58.7
Week 16	61.3	59.2	59.3	58.9
Week 20	61.8	59.9	59.9	59.6
Week 24	62.1	59.9	60.2	59.5
Week 28	62.5	60.2	60.4	60.0
Week 32	62.6	60.2	60.7	59.9
Week 36	62.9	60.2	61.2	59.9
Week 40	62.8	60.5	60.7	59.9
Week 44	63.0	59.9	60.9	59.8
Week 48	62.7	60.6	61.2	59.7
Week 52	63.1	60.4	61.3	60.5

VIEW #2: Mean Change in ETDRS Letter Score from Baseline (Full analysis Set with LOCF)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=296	2Q8 N=306
Week 1	3.4	3.1	3.7	3.2
Week 4	4.8	4.7	5.5	4.5
Week 8	6.5	5.3	6.7	5.7
Week 12	7.4	5.9	7.5	7.2
Week 16	7.5	6.4	7.7	7.3
Week 20	8.0	7.1	8.3	8.0
Week 24	8.3	7.1	8.6	7.9
Week 28	8.7	7.5	8.8	8.4
Week 32	8.9	7.4	9.1	8.3
Week 36	9.1	7.5	9.6	8.3
Week 40	9.1	7.7	9.1	8.3
Week 44	9.2	7.1	9.3	8.2
Week 48	9.0	7.8	9.6	8.1
Week 52	9.4	7.6	9.7	8.9

VIEW #2: Mean Change from Baseline in Visual Acuity through Week 52 by Treatment Group (Full Analysis Set with LOCF)



Additional Efficacy Issues/Analyses

Study VGFT-OD-0702 compared 2 different container closures of the drug product: vial and pre-filled syringe. VGFT-OD-0702 was a single-masked (to the subject), randomized, multi-center clinical study. Subjects were eligible if they had neovascular AMD and completed dosing in VGFT-OD-0502, VGFT-OD-0508, or VGFT-OD-0603 to enroll in this 3 year study to assess the long-term safety and tolerability of repeated IVT administration of VEGF Trap-Eye in subjects with all sub-types of neovascular AMD. Subjects were initially enrolled to receive VEGF Trap-Eye from a Vial. After 152 subjects had been enrolled, a PFS syringe was introduced as a result of Protocol Amendment 1. From that point, upon enrollment, subjects were randomly assigned in 2:1 ratio to receive:

- 2 mg VEGF Trap-Eye PRN in a 50 μL injection volume from a PFS (Single-use, PFS glass syringes with Snap-off Tip Cap. A plastic plunger rod was attached to the rubber stopper inside the barrel of the syringe. After removing the syringe cap, a 30-gauge needle was attached for administration).
- 2 mg VEGF Trap-Eye PRN in a 50 μL injection volume from a Vial (Sealed, sterile 3 mL Vials of approximately 0.5 mL of VEGF Trap-Eye. The VEGF Trap-Eye was withdrawn into a 1 mL syringe using aseptic technique. A sterile 30-gauge needle was used for intravitreal injection).

VGFT-OD-0702: Mean ETDRS Letter Score (Full Analysis Set with LOCF) Cut Off Date 6/28/2010

	Vial N=45	PFS N=87
Baseline	60.2	62.4
Week 8	59.3	62.6
Week 16	60.6	61.7
Week 24	59.9	61.1
Week 32	59.6	60.6
Week 40	60.0	60.6
Week 48	59.1	60.6
Week 56	58.9	60.5
Week 64	58.2	58.8
Week 72	57.1	59.5
Week 80	57.6	59.7
Week 88	56.6	59.6
Week 96	56.8	58.1
Week 104	56.3	58.6
Week 112	56.1	58.6
Week 120	55.2	58.7
Week 128	55.2	58.4
Week 136	55.7	58.3
Week 144	55.6	58.3
Week 152	55.6	58.3
Week 156	55.6	58.3

Mean numbers of injections per subject were similar between the groups (5.8 and 6.2 in the Vial and PFS groups, respectively). The durations that subjects were in the study were similar, with a majority in both groups (74% to 75%) in the study >24 weeks. Mean treatment durations were almost identical between the groups (72.8 to 72.9 weeks). Despite subjects being randomized at different time points, VA over time followed a similar trend in the 2 groups. Most subjects in each group (84% to 87%) maintained vision (<15 letters lost) from baseline of this study to the cut-off date.

Summary Efficacy Statement

Adequate and well controlled studies (VIEW #1, VIEW #2, and VGFT-OD-0702) support the efficacy of aflibercept injection for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD).

When compared to ranibizumab, all 3 doses of VEGF Trap-Eye were non-inferior when comparing the proportion of subjects who maintained vision (lost less than 15 letters lost in the ETDRS letter score). However, none of the doses were superior to ranibizumab.

The current analysis of VIEW #1 and VIEW #2 examined the efficacy of aflibercept at Week 52. The studies are ongoing and efficacy at Year 2 will be available once the studies are completed.

The 2 mg Q 8 weeks dose is recommended for approval and inclusion in the labeling for the aflibercept product. Since the 2 mg Q 8 weeks dose has fewer injections than the other 2 studied doses (2 mg Q 4 weeks and 0.5 mg Q 4 weeks), approval is recommended for this specific dosage which has the theoretical benefit of less injection related risks (i.e. endophthalmitis).

8. Safety

From the original protocols for VIEW 1 and VIEW 2, a serious adverse event is classified as any untoward medical occurrence that at any dose:

- Results in death, or
- Is immediately life threatening at the time of the event, or
  The term 'life threatening' in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability / incapacity, or
- Is a congenital anomaly / birth defect
- Is otherwise considered medically important.

From the original Medical Officer Review:

The main support for safety and efficacy for the AMD indication comes from the following trials: VIEW #1, VIEW #2, and VGFT-OD-0702. In these 3 trials there were a total of 2,614 patients.

Exposure

The following tables present the treatment exposure and duration for all three trials (VIEW #1, VIEW #2, and VGFT-OD-0702).

VIEW #1: Treatment Exposure during the First Year (Safety Analysis Set)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Number of Injections During the First Year Including Sham				
1-4	9	1	11	6
5-8	9	6	5	17
9-13	286	297	288	280
Mean (sd)	12.1 (2)	12.5 (1)	12.1 (2)	12.0 (2)
Number of Injections During the First Year Excluding Sham				
Mean (sd)	12.1 (2)	12.5 (1)	12.1 (2)	7.5 (1)
Total Amount of Study Medication During the First Year in mg				
Mean (sd)	6.0 (1)	24.9 (2)	6.0 (1)	14.9 (2)
Min-Max	1-7	6-26	1-7	2-16

VIEW #1: Treatment Duration (Days) in the First Year (Safety Analysis Set)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Duration of Study Medication (Days)				
Mean (sd)	350.1 (56)	360.0 (27)	347.8 (63)	347.3 958)
Min-Max	28-378	96-378	28-385	28-379

VIEW #2: Treatment Exposure during the First Year (Safety Analysis Set)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=297**	**2Q8 N=307**
Number of Injections During the First Year Including Sham				
1-4	5	10	9	9
5-8	6	12	8	11
9-13	280	287	280	287
Mean (sd)	12.7 (1)	12.6 (1)	12.7 (1)	12.6 (1)
Number of Injections During the First Year Excluding Sham				
Mean (sd)	12.7 (1)	12.6 (1)	12.6 (1)	7.7 (1)
Total Amount of Study Medication During the First Year in mg				
Mean (sd)	6.2 (1)	24.4 (4)	6.2 (1)	15.1 (3)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Min-Max	0.5-8.0	2.0-28.0	0.5-8.0	2.0-34.0

VIEW #2: Treatment Duration in the First Year (Safety Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Duration of Study Medication (Days)				
Mean (sd)	353.3 (47)	346.5 (61)	349.4 (56)	347.6 (62)
Min-Max	28-378	28-400	28-374	28-385

Study VGFT-OD-0702: Treatment Exposure during the First Year (All Randomized Population)

	Vial N=50	PFS N=99
Number of Injections		
Mean (sd)	5.8 (5)	6.2 (5)
Min-Max	0-22	0-23
Total Amount of Study Medication in mg		
Mean (sd)	11.6 (10)	12.4 (10)
Min,Max	0-44	0-46

Study VGFT-OD-0702: Treatment Duration in the First Year (Safety Analysis Set)

	Vial N=50	PFS N=99
Duration of Study Medication in Weeks		
Mean (sd)	72.8 (47)	72.9 (47
Min-Max	0-139	0-140

1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Disposition of Subjects

VIEW #1: Disposition (All Randomized Subjects)

	R0.5Q4	2Q4	0.5Q4	2Q8
Randomized	306	304	304	303
Completed first year of study	284 (92.8%)	293 (96.4%)	277 (91.1%)	276 (91.1%)
Discontinuation from study with first year	22	11	27	27
Adverse event	4	3	5	4
Death	3	1	2	7

	R0.5Q4	2Q4	0.5Q4	2Q8
Withdrawal by subject	10	5	7	8
Protocol deviation	3	0	3	1
Lost to follow-up	1	2	4	4
Treatment failure	0	0	2	2
Other	1	0	4	1

VIEW #2: Disposition (All Randomized Subjects)

	R0.5Q4	2Q4	0.5Q4	2Q8
Randomized	303	313	311	313
Completed first year of study	276 (91.1%)	281 (89.8%)	274 (88.1%)	284 (90.7%)
Discontinuation from study with first year	27	32	37	29
Adverse event	2	6	8	9
Death	1	3	2	1
Withdrawal by subject	11	15	13	11
Protocol deviation	2	1	1	0
Lost to follow-up	4	1	2	2
Treatment failure	0	0	1	1
Other	7	6	10	5

Study VGFT-OD-0702: Disposition (All Enrolled Set)

	N=149
Subjects Prematurely Terminated From Study	28
Withdrawn Due to AE	4
Investigator Decision	2
Subject Request for Withdrawal	8
Lost to f/u	3
Death	7
Other	4

There are no remarkable differences between groups in the disposition of subjects after one year.

Deaths

VIEW #1: Listing of Deaths (Safety Analysis Set)

Subject Number	Treatment Group	Study Day	Number of Days After Last Dose	Cause
145-022	RQ4	19	19	Myocardial infarction
502-001	RQ4	223	83	Hepatic neoplasm

Subject Number	Treatment Group	Study Day	Number of Days After Last Dose	Cause
502-008	RQ4	259	35	Lung neoplasm
506-011	RQ4	259	77	CHF
507-019	RQ4	368	33	Aspiration pneumonia
142-027	2Q4	206	15	COPD
314-002	2Q4		54	Respiratory insufficiency
218-008	0.5Q4	99	13	Cerebral hemorrhage
502-003	0.5Q4	80	53	Myocardial infarction
114-018	2Q8	144	4	Hemorrhagic shock
146-016	2Q8	211	15	CVA
182-002	2Q8	313	33	Myocardial infarction
237-003	2Q8	171	31	Arteriosclerosis
284-002	2Q8	113	29	CHF
305-006	2Q8	150	31	Leukemia
309-009	2Q8	233	9	COPD
505-004	2Q8	257	56	CHF

VIEW #2: Listing of Deaths (Safety Analysis Set)

Subject Number	Treatment Group	Study Day	Number of Days After Last Dose	Cause
160020002	RQ4	398	unknown	Esophageal CA
440030022	RQ4	118	3	Acute MI
240090004	0.5Q4	unknown	unknown	unknown
760010013	0.5Q4	46	18	MI
100220010	2Q4	90	35	CVA
600090017	2Q4	359	77	Pyrexia*
600130001	2Q4	251	58	Cardiopulmonary failure
430060004	2Q8	196	27	Lung CA
600040008	2Q8	60	4	Cardiac arrest

- *This patient had experienced a road traffic accident causing polytrauma a few weeks before that fatal pyrexia.*

Study VGFT-OD-0702: Listing of Deaths

Subject Number	Study Day (relative to first dose)	Number of Days After Last Dose	Cause
001-0112	902	43	Unknown at this time
015-1501	748	216	Stroke
018-1801	725	88	Lung CA
020-2007	946	159	Lung CA
027-2709	1006	670	Myocardial

Subject Number	Study Day (relative to first dose)	Number of Days After Last Dose	Cause
			infarction
028-2806	603	295	Respiratory failure
044-4401	1175	106	Pulmonary edema
005-0504	1101	564	Lung CA

In VIEW #1 there were at total of 17 deaths (5 subjects in the RQ4 group, 2 subjects in the 2Q4 group, 2 subjects in the 0.5Q4 group, and 8 subjects in the 2Q8 group) during Year 1.

In VIEW #2 there was a total of 9 deaths (2 subjects in the RQ4 group, 3 subjects in the 2Q4 group, 2 subjects in the 0.5Q4 group, and 2 subjects in the 2Q8 group) during Year 1.

In Study VGFT-OD-0702, 8 subjects died during the period from baseline of this study to the cut-off date.

The deaths were not considered to be related to therapy.

Common Adverse Events

A treatment-emergent adverse event was defined as an event that was observed or reported after administration of study drug that was not present prior to study drug administration or an event that represented an exacerbation of a pre-existing event.

VIEW #1: Ocular Treatment Emergent AE in the Study Eye Occurring in at Least >=5% of Subjects (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Number of subjects with at least 1 ocular TEAE in study eye	246	228	226	238
Conjunctival hemorrhage	144	109	120	131
Vitreous floaters	33	40	23	21
Eye pain	26	33	27	22
Vitreous detachment	24	26	23	19
Visual acuity reduced	20	24	23	20
Retinal hemorrhage	19	9	17	23
Retinal pigment epitheliopathy	11	16	15	13
Macular degeneration	16	16	17	10
IOP increased	22	14	12	15
Eye irritation	16	13	13	12
Maculopathy	19	10	20	8
FBS	9	8	9	16

VIEW #1: Non-Ocular Treatment Emergent AE in the Study Eye Occurring in at Least >=2% of Subjects (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Number of subjects with at least 1 non-ocular TEAE in study eye	234	220	231	223
Infections	123	96	102	104
Nasopharyngitis	23	33	24	26
Upper respiratory tract infection	13	11	14	18
UTI	17	14	15	13
Bronchitis	16	12	11	17
Sinusitis	8	7	11	11
Influenza	9	7	3	7
Pneumonia	14	5	4	6
Cellulitis	7	3	6	2
Investigations	48	57	59	60
Blood glucose increased	8	9	11	7
Protein urine present	7	7	7	10
Urine protein/creatinine ratio increased	3	6	9	6
Blood urine present	4	7	5	6
Blood pressure increased	4	5	3	9
Nervous system disorders	35	40	47	47
HA	19	11	11	12
Dizziness	5	8	6	7
Injury	42	33	47	45
Fall	15	14	12	16
Contusion	4	1	7	3
GI disorder	52	39	37	40
Nausea	13	12	10	7
Diarrhea	9	11	7	5
GERD	6	2	8	6
Constipation	12	3	5	6
Musculoskeletal disorders	54	30	38	41
Arthralgia	11	10	12	5
Back pain	9	5	6	9
Osteoarthritis	5	1	4	7
Arthritis	9	3	5	2
Respiratory disorders	47	34	25	36

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Cough	11	7	2	10
COPD	6	5	5	7
Dyspnea	8	4	5	3
Cardiac disorders	41	30	29	32
A fib	11	5	4	6
Vascular disorders	34	30	26	28
HTN	25	21	21	20
Metabolism disorders	29	24	26	24
Hypercholesterolemia	5	3	5	7
Skin disorders	22	16	25	20
General disorder and administration site condition	19	20	16	22
Neoplasms	22	15	21	22
Basal cell CA	4	4	8	8
Renal disorders	19	11	19	15
Psychiatric disorders	21	10	15	14
Anxiety	7	2	3	4
Immune disorders	8	10	12	16
Seasonal allergy	4	6	9	9
Blood disorders	10	6	14	9
Ear disorders	7	7	6	11
Vertigo	4	5	3	8
Reproductive disorders	3	4	8	7

VIEW #2: Ocular Treatment Emergent AE in the Study Eye Occurring in at Least >=5% of Subjects (Safety Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Number of subjects with at least 1 ocular TEAE in study eye	187	191	182	198
Visual acuity reduced	20	26	34	33

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Conjunctival hemorrhage	23	24	37	30
Retinal hemorrhage	29	27	30	27
Macular degeneration	23	27	23	30
Eye pain	27	33	22	21
IOP increased	19	24	15	15
Detachment of RPE	15	18	15	12
Vitreous detachment	9	18	9	15
Cataract	15	16	12	12
Ocular hyperemia	18	12	13	9
Retinal degeneration	11	17	9	7

VIEW #2: Non-Ocular Treatment Emergent AE in the Study Eye Occurring in at Least >=2% of Subjects (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Number of subjects with at least 1 non-ocular TEAE in study eye	181	231	206	213
Infections	77	72	67	73
Nasopharyngitis	25	14	25	19
Influenza	7	14	8	17
Bronchitis	7	13	9	9
UTI	9	7	6	5
Cystitis	3	6	6	2
Upper respiratory tract infection	6	3	5	5
Investigations	43	63	55	61
Blood glucose increased	1	12	8	8
EKG T wave inversion	5	9	2	7
Cardiac disorders	32	48	35	40
AV first degree block	10	20	14	9
A fib	3	7	1	5
GI disorders	30	40	34	45
Diarrhea	10	8	10	14
Abdominal pain	0	3	1	1
Vomiting	6	4	3	2
Musculoskeletal disorders	31	36	33	39

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Back pain	13	14	9	11
Arthralgia	8	7	10	3
Osteoarthritis	4	5	5	6
Nervous system disorders	27	33	26	35
HA	11	9	12	17
Dizziness	9	5	1	3
Vascular disorders	247	33	24	23
HTN	22	22	18	16
Respiratory disorders	24	25	25	24
Cough	7	2	7	3
Injury	19	18	26	27
Fall	9	3	4	2
General disorders	**18**	22	29	13
Pyrexia	8	8	15	5
Metabolism disorders	12	19	16	23
DM	4	7	2	7
Hyperglycemia	2	2	6	2
Skin disorders	18	20	14	14
Renal disorders	5	9	11	13
Psychiatric disorders	7	7	11	10
Blood disorders	11	5	12	10
Anemia	6	4	8	7
Neoplasms	6	8	10	8
Ear disorders	4	7	8	9
Reproductive disorders	4	5	4	8
Surgical procedures	4	7	2	3

Study VGFT-OD-0702: Ocular Treatment Emergent AE Reported by >3 Subjects in the Study Eye (All Randomized Set)

	Vial N=50	PFS N=99	Total N=149
Number of subjects with events	38	58	96
Retinal hemorrhage	8	8	16
Cataract	7	9	16
VA reduced	8	7	15
Conjunctival hemorrhage	6	8	14
Vitreous floaters	2	7	9
Blepharitis	5	2	7
Macular degeneration	3	4	7
FBS	0	6	6
Vitreous detachment	5	1	6
Eye pain	1	3	4
Eye pruritis	0	4	4
Injection site pain	0	4	4
IOP increased	0	4	4

Study VGFT-OD-0702: Non-Ocular Treatment Emergent AE Reported by >3 Subjects in the Study Eye Occurring (All Randomized Set)

	Vial N=50	PFS N=99	Total N=149
Number of subjects with events	44	87	131
Blood disorders	1	6	7
Anemia	1	4	5
Cardiac disorders	4	12	16
A fib	2	2	4
Ear disorders	4	3	7
Vertigo	2	3	5
GI disorders	14	28	42
Diarrhea	5	5	10
Nausea	3	4	7
Vomiting	4	1	5
GERD	2	2	4
Dyspepsia	1	3	4
Hepatobiliarty disrders	0	5	5
Cholelithiasis	0	4	4
Immune system disorder	1	9	10

	Vial N=50	PFS N=99	Total N=149
Seasonal allergy	0	7	7
Infections	24	46	70
Nasophayrngitis	5	11	16
Bronchitis	5	9	14
UTI	6	7	13
Sinusitis	2	8	10
Upper respiratory tract infection	4	5	9
Influenza	2	4	6
Pneumonia	2	4	6
Localized infection	0	4	4
Injury	12	23	35
Fall	9	10	19
Contusion	3	2	5
Rib fracture	1	3	4
Investigations	10	32	42
Protein urine present	4	2	6
WBC increased	2	4	6
Blood pressure increased	0	4	4
WBC urine positive	0	4	4
Metabolism disorders	8	14	22
Hypercholesterolemia	2	2	4
DM	2	1	3
Gout	1	2	3
Dehydration	1	1	2
DM inadequate control	0	1	1
Musculoskeletal disorders	13	29	42
Arthritis	2	6	8
Osteoarthritis	4	4	8
Arthralgia	2	5	7
Back pain	2	3	5
Pain in extremity	2	3	5
Osteoporosis	0	4	4
Bursitis	2	2	4
Neoplasm	5	19	24
Basal cell CA	1	5	6
Squamous cell CA of skin	2	2	4
Nervous system disorders	11	21	32
Dementia	2	3	5
Dizziness	1	4	5
Psychiatric disorders	5	11	16
Depression	1	4	5

	Vial N=50	PFS N=99	Total N=149
Insomnia	2	3	5
Respiratory disorders	8	14	22
Cough	3	4	7
Dsypnea	1	3	4
Skin disorders	2	14	16
Rash	0	4	4
Vascular disorders	4	14	18
HTN	1	11	12

The most common adverse reactions (≥5%) reported in patients receiving aflibercept injection were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Drug- Specific Safety Explorations

IMMUNOGENICITY

For both VIEW #1 and VIEW #2 samples for ADA (anti-drug-antibody) were taken at Screening and subsequently on Weeks 12, 24, 36, and 52. All samples were drawn prior to injection of study drug.

VIEW#1: Number of Subjects with Anti-VEGF Trap Antibodies By Treatment Group (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Negative	287	291	290	297
Positive	15 (4.9%)	13 (4.3%)	11 (3.6%)	6 (2.0%)
Not drug induced	5	3	8	5
Transient	7	7	3	1
Persistent	3	3	0	0
Missing*	2	0	3	0

*Subjects with no sample collection of subjects with missing post-baseline sample.

VIEW#2: Number of Subjects with Anti-VEGF Trap Antibodies By Treatment Group (Safety Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Negative	280	285	277	303
Positive	8 (2.7%)	15 (4.9%)	16 (5.4%)	3 (1.0%)

Not drug induced	3	8	8	1
Transient	3	2	4	1
Persistent	2	5	4	1
Not applicable	3	9	4	1

These results show that the observed levels of immunogenicity were relatively low and similar between the different groups, including the RQ4 group in which subjects were not administered aflibercept. Furthermore, some subjects were positive even before exposed to the drug at baseline.

NASOMUCOSAL EXAMINATION (ENT SUB-STUDY)

A subset of 160 subjects in VIEW #2 was additionally examined by an ENT specialist, including nasal endoscopy (ENT sub-study). The purpose of the ENT sub-study was to better define potential nasomucosal side effects which were reported as histopathologic findings in a toxicology study (VGFT-TX-0511 or COV7369-112).

VIEW #2: ENT Sub-Study (Number of Subjects with ENT Treatment Emergent AEs)

	R0.5Q4 N=37	**2Q4 N=42**	**0.5Q4 N=37**	**2Q8 N=44**
Nasal septum deviation	4	2	0	5
Nasal mucosal disorder	1	1	2	4
Rhinorrhea	0	1	2	4
Epistaxis	1	1	1	3
Nasal polyps	1	1	1	2
Nasal turbinate hypertrophy	0	0	1	2
Nasal dryness	0	0	0	1
Nasal mucosal discoloration	0	0	1	1
Nasal edema	0	0	0	1
Paranasal cyst	0	0	1	1
Rhinitis hypertrophy	1	0	0	0
Nasopharyngitis	5	2	4	8
Upper respiratory tract infection	1	1	1	4
Rhinitis	2	0	1	1
Viral rhinitis	0	0	1	1
Acute tonsillitis	1	0	0	0

The results of the ENT Sub-study in 160 patients at year 1 did not show an increased rate of nasal erosions or other ENT conditions associated with aflibercept compared to ranibizumab.

ARTERIAL THROMBOEMBOLIC EVENTS

VIEW#1: Number of Subjects with APTC Arterial Thromboembolic Events Through Year 1 (Safety Analysis Set)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Any APTC event	5 (1.6%)	2 (0.7%)	7 (2.3%)	6 (2.0%)
Non-fatal myocardial infarctions	4	1	4	1
Non-fatal strokes	0	1	2	1
Vascular deaths	1	0	1	4

VIEW#2: Number of Subjects with APTC Arterial Thromboembolic Events through Year 1 (Safety Analysis Set)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=297**	**2Q8 N=307**
Any APTC event	5 (1.7%)	4 (1.3%)	5 (1.7%)	8 (2.6%)
Non-fatal myocardial infarctions	2	2	2	5
Non-fatal strokes	2	1	1	2
Vascular deaths	1	1	2	1

Arterial thromboembolic events were a pre-specified AE of interest because of the association of thromboembolic events and VEGF inhibitors. There was no statistically significant difference between groups. There is no clear trend indentified for a particular dose or interval.

INTRAOCULAR PRESSURE

VIEW #1: Number of Subjects with an Absolute Value of IOP >= 35mmHg During the Study (Safety Analysis Set)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Any Visit	13	13	7	13

VIEW #2: Number of Subjects with an Absolute Value of IOP >=35mmHg During the Study (Safety Analysis Set)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=297**	**2Q8 N=307**
Any Visit	9	9	4	5

VIEW #1: Proportion of Subjects with >=10mmHg Increase in IOP from Baseline to Any Pre-Dose Measurement (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Pre-dose from baseline	12	5	6	7

VIEW #2: Proportion of Subjects with >=10mmHg Increase in IOP from Baseline to Any Pre-Dose Measurement (Safety Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Pre-dose from baseline	7	3	8	7

VIEW #1: Proportion of Subjects with >=10mmHg Increase in IOP (Safety Analysis Set)

		R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Baseline	Post-dose from pre-dose	24	28	14	25
Week 1	Pre-dose from baseline	1	1	0	0
Week 4	Pre-dose from baseline	0	0	0	2
	Post-dose from pre-dose	23	28	24	24
Week 8	Pre-dose from baseline	2	1	1	0
	Post-dose from pre-dose	25	26	20	27
Week 12	Pre-dose from baseline	0	0	1	0
	Post-dose from pre-dose	19	27	25	0
Week 16	Pre-dose from baseline	0	0	1	2
	Post-dose from pre-dose	27	27	25	16
Week 20	Pre-dose from baseline	1	0	0	1
	Post-dose from pre-dose	24	28	17	5
Week 24	Pre-dose from baseline	1	0	2	1
	Post-dose from pre-dose	15	36	17	25
Week 28	Pre-dose from baseline	2	0	1	0
	Post-dose from pre-dose	20	22	18	9
Week 32	Pre-dose from baseline	0	2	3	1

		R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
	Post-dose from pre-dose	23	29	15	32
Week 36	Pre-dose from baseline	1	1	0	2
	Post-dose from pre-dose	31	28	22	1
Week 40	Pre-dose from baseline	2	1	1	2
	Post-dose from pre-dose	25	32	18	21
Week 44	Pre-dose from baseline	1	0	0	0
	Post-dose from pre-dose	17	29	18	5
Week 48	Pre-dose from baseline	0	0	1	2
	Post-dose from pre-dose	23	17	19	31
Week 52	Pre-dose from baseline	4	0	1	1
	Post-dose from pre-dose	4	2	4	4

VIEW #2: Proportion of Subjects with >=10mmHG Increase in IOP (Safety Analysis Set)

		R0.5Q4 N291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Baseline	Post-dose from pre-dose	8	10	2	8
Week 1	Pre-dose from baseline	0	0	1	3
Week 4	Pre-dose from baseline	1	0	0	0
	Post-dose from pre-dose	5	11	3	8
Week 8	Pre-dose from baseline	1	0	1	0
	Post-dose from pre-dose	8	8	5	12
Week 12	Pre-dose from baseline	1	0	1	1
	Post-dose from pre-dose	7	8	7	1
Week 16	Pre-dose from baseline	0	0	2	2
	Post-dose from pre-dose	12	6	7	7
Week 20	Pre-dose from baseline	1	0	0	2
	Post-dose from pre-dose	13	8	2	1
Week 24	Pre-dose from baseline	0	0	1	0
	Post-dose from pre-dose	8	5	5	6
Week 28	Post-dose from pre- dose	8	10	4	1
Week 32	Post-dose from pre-dose	6	7	6	5

		R0.5Q4 N291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Week 36	Pre-dose from baseline	2	0	0	3
	Post-dose from pre-dose	10	9	4	2
Week 40	Pre-dose from baseline	2	1	1	1
	Post-dose from pre-dose	7	7	3	7
Week 44	Pre-dose from baseline	1	0	0	0
	Post-dose from pre-dose	8	6	6	1
Week 48	Pre-dose from baseline	2	1	3	1
	Post-dose from pre-dose	8	7	5	3
Week 52	Pre-dose from baseline	0	0	1	1
	Post-dose from pre-dose	3	0	1	2

Elevations in IOP following repeated dosing of VEGF-inhibitors has been reported in the literature.

There was no clear trend observed between groups in IOP elevation. The majority of IOP increases appeared to be post-dose measurements and secondary to the injection procedure itself.

Safety Summary Statement

The 12-Month Clinical Study Reports submitted within this BLA 125387 for VIEW #1, VIEW #2, and VGFT-OD-0702 support the safety of aflibercept injection in the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD).

The most common adverse reactions (≥5%) reported in patients receiving aflibercept injection were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Observed levels of immunogenicity were relatively low and similar between the different groups, including the ranibizumab Q 4 week group in which subjects were not administered aflibercept.

The results of the ENT Sub-study in 160 patients at year 1 did not show an increased rate of nasal erosions or other ENT conditions associated with aflibercept compared to ranibizumab.

There was no statistically significant difference between groups in arterial thromboembolic events. There was no clear trend indentified for a particular dose or interval.

The majority of IOP increases appeared to be post-dose measurements and secondary to the injection procedure itself.

The 2 mg Q 8 weeks dose is recommended for approval and inclusion in the labeling for the aflibercept product. Since the 2 mg Q 8 weeks dose has fewer injections than the other 2 studied doses (2 mg Q 4 weeks and 0.5 mg Q 4 weeks), approval is recommended for this specific dosage which has the theoretical benefit of less injection related risks (i.e. endophthalmitis).

In an eventual Postmarketing Requirement, the applicant should provide clinical information from a 1-year (minimum) clinical study to support that there are no adverse effects on the corneal endothelium in 100 eyes (minimum) following the intravitreal administration of aflibercept.

9. Advisory Committee Meeting

The Dermatologic and Ophthalmic Drugs Advisory Committee of the Food and Drug Administration met on June 17, 2011, at the Marriott Inn and Conference Center University of Maryland University College (UMUC), Adelphi, Maryland. Michael X. Repka, M.D., chaired the meeting.

Attendance:
Dermatologic and Ophthalmic Drugs Advisory Committee Members present (voting):
Lynn A. Drake, M.D. ,Lynn K. Gordon, M.D., Ph.D., Susan M. MacDonald, M.D., Mary A. Majumder, Ph.D. , Michael X. Repka, M.D. (Chair) , Allan R. Rutzen, M.D.
Temporary Voting Members:
Marcia D. Carney, M.D. Donald Fong, M.D., M.P.H. Laina King, Ph.D. (Patient Representative), Charles A. Rohde, Ph.D.
Industry Representative (non-voting):
Ellen Strahlman, M.D., M.H.Sc
FDA Participants (non-voting):
Edward M. Cox, M.D., MPH; Wiley Chambers, M.D., Sonal Wadhwa, M.D., Dongliang Zhuang, Ph.D.

The following questions were presented to the committee:

1) Do you think adequate safety and efficacy for aflibercept injection has been demonstrated for the treatment of neovascular AMD?

The committee unanimously (all 10 voting members) agreed that adequate safety and efficacy for aflibercept injection has been demonstrated for the treatment of neovascular age-related macular degeneration.

2) If yes, on which study(ies) are you basing your decision?

The majority of the committee based their decision on both View# 1 and View#2 studies.

3) If not, what additional study(ies) should be performed? Do you have any suggestions regarding trial design?

Not applicable.

4) What dosing should be approved (0.5mg Q4, 2mg Q4, or 2mg Q8)? If recommend approving a Q8 schedule should patients be monitored Q4?

The committee recommended 2mg every eight weeks (Q8) with an extra dose at month 2 (2mg monthly for 3 months then once every 2 months). The majority of the committee agreed that monitoring should be at the discretion of the physician and not be required.

5) Elevations in IOP following repeated dosing of VEGF-inhibitors has been reported in the literature and is seen in low frequency in the trials of aflibercept, do you have recommendations of ways to handle the issue?

No recommendations.

6) Do you have any suggestions concerning the proposed draft labeling of the product?

In summary, the committee suggested the following:

- In the dosage and administration section, state the loading dose of 3 initial monthly injections of 2mg first, then 2mg once every 2 months.
- The refrigerated temperature range should be defined.
- Information on how to switch patients from previous VEGF inhibitor medications to aflibercept.

10. Pediatrics

The population studied for this indication was predominantly in the 7th and 8th decades of life reflective of the population most affected by this disease. The demographics of the patients enrolled in the trial during the development program for this proposed indication are representative of the targeted population.

The applicant requested a waiver of the pediatric study requirements (b) (4) for this original Biologics License Application. The waiver was requested because the disease under study (Neovascular (Wet) Age-Related Macular Degeneration (AMD)) does not exist in children.

This BLA was presented at the Pediatric Review Committee (PeRC) on June 1, 2011. The PeRC agreed with the Division to grant a full waiver for this product.

11. Other Relevant Regulatory Issues

BIOSTATISTICS

Per the original Biostatistics review:

The BLA application was mainly supported by the clinical data from two Phase-3 studies, VGFT-OD-0605 (VIEW 1) and 311523 (VIEW 2). These studies demonstrated that VEGF Trap-Eye is non-inferior to 0.5 mg ranibizumab with respect to the proportion of subjects who maintained vision at week 52, based on a non-inferiority margin of 10%. In both studies, nearly 94% of subjects treated with VEGF Trap-Eye and 0.5 mg ranibizumab maintained vision at week 52. Furthermore, the design and conduct of both non-inferiority studies for the VEGF Trap-Eye program are considered adequate.

Table 1: Key efficacy results at week 52 - proportion of subjects who maintained vision, change in BCVA score from baseline, and proportion of subjects who gained ⩾15 letters in BCVA score from baseline (Full analysis set)

Treatment	Number of subjects	Subjects who maintained vision (%)	Mean (SD): number of letters	Gain of ≥ 15 letters (%)
Ranibizumab 0.5Q4	304	93.8%	8.1 (15.2)	30.9%
VTE 2Q4	304	95.1%	10.9 (13.8)	37.5%
VTE 0.5Q4	301	95.0%	6.9 (13.4)	24.9%
VTE 8Q4	301	94.4%	7.9 (15.0)	30.6%
Ranibizumab 0.5Q4	291	94.8%	9.4 (13.5)	34.0%
VTE 2Q4	309	94.5%	7.6 (12.6)	29.4%
VTE 0.5Q4	296	95.3%	9.7 (14.1)	34.8%
VTE 8Q4	306	95.4%	8.9 (14.4)	31.4%

Note: Maintenance of vision was defined as a loss of <15 letters in the ETDRS letter score.
Source: VGFT-OD-0605 (VIEW 1) CSR Tables 20, 22, and 23; 311523 (VIEW 2) CSR Tables 21, 24, and 25.

In the Reviewer's view, the efficacy of VEGF Trap-Eye compared to 0.5 mg ranibizumab for treatment of neovascular AMD had been adequately demonstrated in the Phase-3 studies included in the application.

CDRH CONSULTATION

In a consultation request dated May 27, 2011, the Product Quality reviewer requested that the Center for Devices and Radiological Health:

(b) (5)

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) attended team

(b) (5)

meetings for the aflibercept appliation and participated in preliminary internal labeling discussions. They did not complete a formal review of the packaging or label this review cycle.

DDMAC had no concerns regarding the proposed name, Eylea, from a promotional perspective.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Eylea, on May 25, 2011. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional. DMEPA had no objection to the proprietary name, Eylea, at this time.

DMEPA finalized their review of the Eylea carton and container labeling on August 5, 2011.

The current labeling for Eylea found in this Cross-Discipline Team Leader Review (see Appendix 3) is draft.

FINANCIAL DISCLOSURE
Regeneron has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There is no evidence to suggest that the results of the studies were impacted by any financial payments.

OSI
An Office of Scientific Investigations (OSI) audit was requested.

Per the OSI review dated July 18, 2011:

Three clinical site inspections were conducted in support of this application. No significant regulatory violations were noted at Dr. Prema Abraham's site (VIEW #1, 142), and although regulatory violations were noted at Drs. Jeffrey Heier's (VIEW #1, 146) and Mark Michels' (View #1, 114) sites, the findings are unlikely to significantly impact data reliability.

In general, inspection of Dr. Abraham's site revealed that the study appears to have been conducted adequately and the data appear reliable in support of the BLA. The final classification for the inspection of Dr. Abraham is No Action Indicated (NAI).

Inspection of Dr. Heier's site documented regulatory violations including failure to ensure the investigation was conducted in accordance with the investigational plan. Informed consent was obtained by a non-IRB approved employee, and this employee erroneously completed the legally authorized representative area of the informed consent. Although these regulatory violations were noted at this site, it is unlikely that these findings would affect subject data, reliability or integrity. In addition, a subinvestigator switched roles in violation of the protocol

from masked to unmasked resulting in unblinding of Subjects #1, 3, 6, and 8. The final classification for the inspection of Dr. Heier's site is Voluntary Action Indicated (VAI).

Regulatory violations documented at Dr. Michels' site initially raised concerns regarding the lack of documentation that subjects met inclusion and exclusion criteria, use of non-IRB approved promotional material for subject recruitment, and lack of documentation of use of the appropriate informed consent document. OSI submitted an Information Request to the Applicant requesting that they provide angiographic measurements to determine eligibility. In an email dated July 11, 2011, the Applicant provided the angiographic data measurements and description of eligibility based on DARC assessment and enrollment at Dr. Michel's site. Although several significant regulatory violations were noted during the inspection including lack of documentation that subjects met inclusion and exclusion criteria at Dr. Michels' site, the sponsor has provided adequate information and documentations showing that subjects at Dr. Michels' site were eligible for enrollment. Given the additional information provided by the applicant and review of Exhibits in the EIR, the observations at Dr. Michels' site do not appear to significantly impact data integrity or subject protection. The preliminary classification for this inspection is VAI.

From an internal email from OST dated 8/2/2011:

The inspection of the sponsor, Regeneron Pharmaceuticals, Inc., has been completed on July 29, 2011. There was no FDA 483 issued to the sponsor.

12. Labeling

The labeling submitted by Regeneron on July 19, 2011, has been edited.

A track changes version of the Agency edits to this July 19th Regeneron label are found in this Cross-Discipline Team Leader Review (see Appendix 3). This label is acceptable as a working draft. This is not a final label.

Carton and container labeling has not been finalized.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
BLA 125-387 for Eylea (aflibercept injection) is not recommended for approval. Although the clinical studies contained in this submission support the use of aflibercept injection for the treatment of neovascular AMD, there are outstanding product quality and drug product microbiology deficiencies.

Recommend [redacted] (b) (5) the following deficiencies (in italics):

PRODUCT QUALITY

1. *Regarding the cell banks:*

[redacted] (b) (4)

2. *As currently presented, it is not possible to assess the appropriateness of most of the in process controls (IPCs) identified in section 3.2.S.2.2.*

a. *Provide data to support the IPCs. For each IPC, historical data for each lot that was used for calculating mean should be presented; the IPC historical range, mean, and standard deviation (SD) should also be included.*
b. *For those IPC limits set using historical mean* (b) (4) *provide justification for setting IPC limits based on* (b) (4) *SDs.*
c. *Describe the actions taken for out-of-trend excursions (IPC values that fall outside the internal action limits). Identify any IPC that would not follow the general OOT actions and the action(s) that would be taken. For example, excursions past the limit of in vitro cell age (LIVCA), which is based on LIVCA validation data in the BLA, would require submission of a supplement supporting a new LIVCA prior to product release and should not be administered only through a general established deviation procedure and your QA release process.*
d. *Section 3.2.S.2.4.1 (p. 11) states that "IPCs with limited predictive power will be removed from consideration." The IPCs identified in section 3.2.S.2.2 should not be removed without the proper submissions to the BLA.*

3. *For DS process validation:*

(b) (4)

(b) (4)

(b) (4)

[redacted]

d. Regarding hold time:

i. Provide data supporting the hold time validation acceptance criteria.

ii. Submit results (raw data) from IEF testing for the samples that did not meet acceptance criteria for hold time validation.

(b) (4)

[redacted]

(b) (4)

v. Table 13 in section 2.3.S.2 lists the completion status of processing hold times as "concurrent validation." Please clarify your intentions. Until validation of hold times is complete and data are submitted to the BLA, the hold times may not be considered part of the approved BLA process.

vi. For (b) (4) *hold times, it is stated that microbial results met their acceptance criteria "demonstrating that the evaluated hold times are acceptable for this process" (section 3.2.S.2.5.7 p. 108). However, product quality assessment was included in the study design and testing is "currently in progress." Therefore, the hold time validations are not complete, and the hold times will not be acceptable as part of the approved BLA process.*

vii. Regarding media hold times (Table 78, section 3.2.S.2.5.7, p. 109), bioburden acceptance criteria are presented; however, footnote "a" states that "a bioburden specification is not applicable." The media and media solution hold studies are performed to ensure that the hold times and conditions are appropriate with respect to the quality of the solutions for use in manufacture; bioburden is a critical parameter for media and solutions, and therefore should be included in these hold studies. Hold times should be based on materials prepared and stored as they would be for use in manufacturing. Therefore, the media and solutions should be filtered and stored under conditions comparable to those used during the manufacturing process, and appropriate bioburden criteria should be set and met. Provide appropriate media and solutions hold times and validation data to justify these times.

(b) (4)

f. The section on Leachates from Contact Surfaces (3.2.S.2.5.9) does not provide any information on the assessments made for the components used and gives the impression that this assessment has not yet been done for the current process. Identify whether assessment of leachates for contact surfaces has been finalized and include the evaluation results for those products/steps requiring further evaluation based on your decision process.

g. Regarding the production-scale conformance batches:

i. Provide the validation protocols, including acceptance criteria.

ii. Provide the genealogy for all batches from C07003 through C07006. (b) (4) (b) (4)

iii. Provide data justifying the use of [redacted] *outside of the historical average for those situations where* (b) (4) *was used.*

iv. Provide all the validation data, including all operating parameters, performance values, and quality assessments. Include a column containing the historical ranges for each.

v. The action limits for operation and performance values were not discussed; identify any results that were outside the action limits that were identified in section 3.2.S.2.4.

vi. Your conclusion of the performance results for DS intermediate (section 3.2.S.2.5.11.1, p. 125) is that "in total, the outlying performance results comprised less than (b) (4) *of the total results evaluated. These data suggests that the performance of the aflibercept manufacturing process is highly consistent." This statement is not supported by the information provided as this is not the total of the outlying performance results but is the performance results with particular results excluded. Two paragraphs earlier, it is stated that "in total, 123 of 2472 performance results (72 of 616 performance parameters) fell outside the* (b) (4) *standard deviation historical limits." Therefore, the actual outlying performance results comprised* (b) (4) *of the total results evaluated. No data were provided to allow an assessment of the results that were excluded. In your response to item g(iii), identify those datapoints that were excluded. For each of these datapoints, provide a justification for the validity of its exclusion.*

vii. Clarify why there is a minimum load requirement for the (b) (4) (b) (4) (b) (4) *(section 3.2.S.2.5.10.2, p. 133).*

viii. Provide good quality reproductions of the IEF gels and individual band quantitation data for the conformance lots and any additional lots from which data will be used for setting specification acceptance criteria.

4. Regarding DS characterization:

a. Provide data for characterization of higher order (secondary/tertiary) structure in addition to the disulfide bonding assessment obtained using peptide mapping.

b. Regarding MALLS analyses:

i. Provide justification of (b) (4) *for performing an assessment to detect high molecular weight species. Include any data identifying if there are HMW species that are no longer detected* (b) (4)

ii. Provide enlargements of the entire chromatograph for SEC-MALLS (b) (4)

c. Regarding MS analysis:

i. Provide results from a blank run.

ii. Provide an enlarged view of the spectra surrounding the main aflibercept peaks and clarification of the "satellite" peaks/deconvolution artifacts.

[redacted] (b) (4)

e. Provide relative percentage data for [redacted] (b) (4) *for each of the lots assessed.*

f. Provide the complete integrated peak area analyses for [redacted] (b) (4) *In addition, there are unidentified peaks with percent areas that appear to be greater than* [redacted] (b) (4) *based on the apparent size of* [redacted] (b) (4) *identification of such peaks should have been determined. Submit data on all these peaks and the complete integrated peak area analysis to the BLA.*

g. Provide the VEGF165 binding stoichiometry data for lot C08001M440.

h. [redacted] (b) (4) *and* [redacted] (b) (4) *should be assessed as process related impurities; there is no discussion of either of these cell culture components in either the validation section or the impurities section. Provide data regarding the amount present in drug substance or validate clearance of these process related impurities by the purification process.*

[redacted] (b) (4)

j. Regarding product size-related impurities:

i. It is stated in section 3.2.S.3.2.3.1.2 (p. 26) that all [redacted] (b) (4) *(including* [redacted] (b) (4) *were "determined to possess the correct, predicted N-terminal sequence of aflibercept." However, Table 13 of that section states that the N-terminal sequence of* [redacted] (b) (4) *was "not determined." Clarify this discrepancy.*

ii. Table 13 lists only 3 N-terminal sequences for the non-reduced [redacted] (b) (4) *species* [redacted] (b) (4)*, while an additional sequence with truncation at* [redacted] (b) (4) *is listed in Table 12. It is not clear which species corresponds to the structure depicted for the* [redacted] (b) (4) *species. Please clarify.*

iii. Provide information regarding the locations of the truncations for species that initiate at the N-terminus.

iv. Provide to section 3.2.S.3.2.3.2 Table 14 the results for % aggregate for all lots, as these data should be available, and update the aggregation range to include the additional data.

[redacted] (b) (4)

[redacted] (b) (4) *There appear to be HMW bands in the reduced SDS-PAGE gel shown in Figure 7 (section 3.2.S.3.2.3.1.2). However, in section 3.2.S.3.2.3.2 (p. 34), it is stated that "the lack of high molecular weight species in SDS-PAGE analysis suggests that aflibercept aggregates formed under stress conditions are reversible in SDS-PAGE and non-covalent in nature." It appears that there are discrepancies in the identification of the nature of the aflibercept aggregates; in addition, SDS-PAGE analyses of material stored under stress conditions are not described in this section. Clarify the apparent discrepancies and include data supporting the statements and conclusions made.*

k. *ISOQUANT analysis was used for the characterization of deamidation. Given that deamidation of asparagine can result in non-isomerized aspartate, and, therefore, that this assay would not monitor all potential deamidation reactions, provide information on non-isomerized forms of deamidated species that may be present.*

5. *Regarding specifications:*
   a. *Provide justification for a proposed bioassay acceptance criterion of* [redacted] (b) (4) *for DS intermediate, when the proposed acceptance criterion for DS is* [redacted] (b) (4)
   b. *Provide justification for a proposed charge heterogeneity acceptance criterion of* [redacted] (b) (4) *for DS intermediate, when the proposed acceptance criterion for DS is* [redacted] (b) (4)
   c. *Provide justification for the proposed DS protein concentration acceptance criterion* [redacted] (b) (4)
   d. *Describe and justify the use of stability data for setting proposed acceptance criteria for release (section 3.2.S.4.5.1). Include an assessment of how release at extremes that are supported by stability data would not allow for failure of aflibercept by the expiration timeline.*

6. *Regarding analytical procedures:*
   a. *Clarify the statement that appearance and color and pH methods are "based on" USP and Ph. Eur. If different from the compendial method, provide information on the changes from compendia and the validation data where appropriate.*
   b. *Provide data supporting the use of* [redacted] (b) (4) *for the SEC assay that is intended to monitor levels of aggregate.*

7. *Provide batch analysis data for all DS intermediate lots and equivalent lots used as* [redacted] (b) (4)

8. *Regarding reference standard (RS):*
   Characterization results for the current RS lot [redacted] (b) (4) *at qualification and data from earlier RS lots at the 24 month stability time point (section 3.2.S.5.1.3, Table 3) show that the molecular weights for HMW species and main species determined by SEC-MALLS were significantly lower for the 24 month stability samples than for the*

fresh qualification sample, indicating that there could have been an [redacted] (b) (4) *change in each monomer during storage. Address the apparent instability of the RS under its storage condition of -80°C.*

9. *Regarding DS container closure:*
   a. *Regarding the microbial aerosol challenge (section 3.2.S.6.1.7.3), identify the manufacturing steps involving* [redacted] (b) (4) *and justify the use of* [redacted] (b) (4) *during container closure integrity testing. Clarify if step 18.3.2 of batch record document number MR1054, describing* [redacted] (b) (4) *is the same as the* [redacted] (b) (4)
   b. *Justify the use of the* [redacted] (b) (4) *leachable/extractable testing (section 3.2.S.6.1.4, Table 2).*
   c. *Clarify the calculation of* [redacted] (b) (4) *(3.2.S.6.1.4.2, p. 7), as the FTIR results listed in Table 4 are significantly higher than* [redacted] (b) (4)
   d. *Justify the methods used for concentration of samples from extractables testing, given that the concentration methods could lead to loss of some types of extractables.*

10. *Regarding DS stability:*
    a. *For SDS-PAGE and IEF testing, provide good quality reproductions of the gels containing the first and last available timepoints for all lots on stability.*
    b. *Provide freeze-thaw stability data for DS intermediate and DS. Alternatively, provide the controls that are in place to prevent thawed DS intermediate or DS from being refrozen and thawed again for use in future manufacturing.*

11. *Regarding the post-approval stability protocol and stability commitment:*
    We note that drug substance stability allows [redacted] (b) (4) *Identify the causes for this change in protein concentration. We also note that color and appearance are not tested to the same criteria at stability as at release. Please justify these differences.*

12. *Provide stability data for all formulated bulk lots tested. Include data for all timepoints available and provide good quality reproductions of SDS-PAGE and IEF gels for the first and last available timepoints for each of the lots.*

13. *Your formulation development studies to support upper and lower ranges and effect on product quality are ongoing. Very limited data were submitted to the BLA in section 3.2.P.2.1.4. Conclusions made based on these limited data need further justification:*
    a. *Provide updated stability data and justification of conclusions made based on only 2 months of real time data. The submitted 1st and 2nd month timepoints for the "proven acceptable range" studies have no potency assessments for any of the completed portions of the study or for any available time point for the real time or accelerated portions of the study, no SDS-PAGE or IEF assessments for the real time or accelerated portions of the study, and no instron, imaged microscopy, or FTIR assessments. Provide updated data to this section.*

b. *The studies for assessment of effects of* [redacted] (b) (4) *on product quality are not complete. Provide updated data to this section. In addition, provide justification for the filtering of data to exclude* [redacted] (b) (4)

c. *Update the data from the studies assessing effects of* [redacted] (b) (4) *on product quality.*

d. *Update the data from the studies assessing the effects of manufacturing steps on product quality.*

e. *Regarding the assessment of effects of exposure to* [redacted] (b) (4) *on stability, section 3.2.P.2.2.1.7.3 states that the control was DP that was "not exposed to* [redacted] (b) (4) *steel." Clarify this statement; i.e. was DP manufactured without the use of* [redacted] (b) (4) (b) (4)

14. *Regarding manufacturing process development:*

a. *On the subject of comparability:*

i. *The comparative stability study was not complete at the time of BLA submission.* [redacted] (b) (4) (b) (4) *Regarding the decay profiles, as no primary data were provided, the degradation profile of individual aspects (e.g. the identity of HMW variants, LMW variants, charge variants that are generated) cannot be assessed; provide appropriate data to the BLA for review.*

iii. *Provide assessments of rates of degradation for the stressed (45°C) stability comparability studies based on statistical analyses.*

iv. *Provide data with respect to charge variants supporting the comparability of stability of DP in vials* (b) (4) [redacted] (b) (4)

(b) (4)

(b) (4)

(b) (4)

15. *There are inconsistencies among the quality overall summary (2.3.I) Table 1, the manufacturer information in sections 2.3.P and 3.2.P, and the attachment to FDA Form 356h regarding manufacturers and the activities occurring at each manufacturing site. Update all of the sections to reflect the correct manufacturing and testing activities occurring at each site for each of the drug product presentations.*

(b) (4)

(b) (4)

17. *Regarding controls of critical steps and intermediates:*
    a. *Submit formulated bulk stability data for all lots placed on stability. Include all time points available.*
    b. *In sections 3.2.P.3.4, it is not clear what type(s) of limit are associated with the given parameters and criteria. The limits are listed as action limits in section 3.2.P.3.3. Clarify and discuss the action taken.* (b) (4) (b) (4) (b) (4)

18. *Regarding process validation*
    a. *Formulated bulk –* (b) (4) (b) (4)

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[redacted] (b) (4)

ix. The (b) (4) *vial* [redacted] (b) (4) *validation protocols and reports (PVP-R-MA-VITV-3.0, PVR-R-MA-VITV-3.0/4.0/7.0, respectively) state that "the time and distance covered by this route also validates shipments between any other locations within this shipping distance." Provide justification for this statement, as the time/distance could allow for shipping to locations outside this climate zone, and validation of the shipper's ability to hold the 2-8°C temperature under high temperature conditions or without access to a power supply has not been provided. Alternatively, identify how deviations due to such variables are controlled by your process.*

x. Provide an assessment of potential adverse effects on product quality caused by [redacted] (b) (4) *based on the pre-sterilization values, not the lot release acceptance criteria as shown in sections 3.2.P.3.5.1.2 (Table 7) and 3.2.P.3.5.1.2 (Table 4). The fact that test results that are still within release specification acceptance criteria do not indicate that the sterilization process did not affect the product.*

19. Regarding control of drug product:

[redacted] (b) (4)

(b) (4)

20. *According to the container closure section for (b) (4) vials (3.2.P.7 p.5), the secondary packaging contains one vial, one filtration needle, and one package insert; there is no mention of a syringe or delivery needle. Clarify the contents of the final packaging.*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

MICROBIOLOGY/ STERILITY

1. *The shipping validation information indicates that due to the damage observed after* (b) (4) *the blister pack design will be modified and the shipping validation studies will be repeated.*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

4. *Define the acceptable ranges for temperature, humidity, and chamber pressure for the* (b) (4)

5. *Regarding the cycle development and process validation studies for* (b) (4) (b) (4) (b) (4)

6. *Provide the sensitivity of the bubble leak test for package integrity in terms of the breach size detectable.*

(b) (4)

8. *Regarding container closure integrity testing of drug product in vials:* (b) (4)

   b. *Indicate whether container closure integrity has been validated for the* (b) (4) (b) (4) *vials using worst-case filling speed and crimping forces.*
   c. *Provide the bacterial concentration at the end of the microbial ingress tests performed for the* (b) (4)4) *vials.*

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(b) (4)

16. *Insufficient information is provided for the sterility test method* (b) (4)

(b) (4)

(b) (4)

ADDITIONAL INFORMATION

In addition, although necessarily not required to be submitted prior to approval, we request that you provide the following information. If the information cannot be provided prior to an approval, this additional informatin would likely result in requests for postmarketing commitments.

1. *Performance of the container closure integrity test in lieu of the sterility test for drug product stability samples at expiry is recommended.*

(b) (4)

3. *Regarding hold time validation studies performed at* (b) (4), *hold time studies for microbial control at scale is facility-specific and should be performed for each facility even if the processes are the same and identical equipment is used. Provide at scale end of hold bioburden and endotoxin data from three lots of drug product manufactured at the* (b) (4) (b) (4)

4. *Regarding reference standard (RS):*
   In section 3.2.S.5.1.2 Regeneron states that Qualification of future lots of reference standard will be performed using the commercial specifications. Please be aware that

qualification of a RS based on the lot release acceptance criteria is not necessarily acceptable. Criteria must be in place to prevent drift in product quality. For example, assays that use RS as a comparator, such as the potency assay, would require a new RS to be very similar to the existing reference standard, and those requirements should be reflected in the protocol for qualification of a new RS. Please note that release of new RS would require submission of the protocol and data to the BLA for approval prior to use.

(b) (4)

(b) (4)

7. *Removing the Reference Standard (RS) from use because it is no longer representative of the manufacturing process may not necessarily be needed. If the product is considered comparable following the change in the manufacturing process, the RS generated from the previous process should still be an appropriate RS; in addition, a change in RS at the change in the process has the potential to lead to additional drift in the released product. Provide justification for generating a new RS in response to a manufacturing process change. Identify the mechanisms that would assure that a new RS would not cause drift, especially in circumstances that use the RS as comparator for release testing.*

8. *Drug substance intermediate* (b) (4) (b) (4) *Include Drug substance intermediate in the post approval annual stability protocols.*

FDAAA RELATED REQUIREMENT:

Although not necessarily required prior to the approval, you will need to submit data on endothelial cell counts in patients treated with Eylea for a period of at least 11 months and submit that information to the application for our review.

The labeling submitted by Regeneron on July 19, 2011, has been edited.

A track changes version of the Agency edits to this July 19th Regeneron label are found in this Cross-Discipline Team Leader Review (see Appendix 3). This label is acceptable as a working draft. This is not a final label.

Carton and container labeling has not been finalized.

RISK BENEFIT ASSESSMENT:
Although the clinical studies contained in this submission support the safe and effective use of aflibercept injection for the treatment of neovascular AMD, there are outstanding product quality and drug product microbiology deficiencies.

Adequate and well controlled studies (VIEW #1, VIEW #2, and VGFT-OD-0702) support the efficacy of aflibercept injection for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD). When compared to ranibizumab, all 3 doses of VEGF Trap-Eye were non-inferior when comparing the proportion of subjects who maintained vision (lost less than 15 letters lost in the ETDRS letter score). However, none of the doses were superior to ranibizumab. The current analysis of VIEW #1 and VIEW #2 examined the efficacy of aflibercept at Week 52.

The 2 mg Q 8 weeks dose is recommended for inclusion in the labeling for the aflibercept product. Since the 2 mg Q 8 weeks dose has fewer injections than the other 2 studied doses (2 mg Q 4 weeks and 0.5 mg Q 4 weeks), this regimen is recommended based on the theoretical benefit of less injection related risks (i.e. endophthalmitis).

The 12-Month Clinical Study Reports submitted within this BLA 125387 for VIEW #1, VIEW #2, and VGFT-OD-0702 support the safety of aflibercept injection in the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD). The most common adverse reactions (≥5%) reported in patients receiving aflibercept injection were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Product Quality and Drug Product Microbiology Reviewers do not recommend approval for this product.

Clinical, Pharmacology/Toxicology, Clinical Pharmacology, and Drug Substance Product Quality Microbiology have recommended approval for this application.

The Biostatistics consultative review states that the efficacy of aflibercept compared to 0.5 mg ranibizumab has been adequately demonstrated for treatment of neovascular AMD in the Phase-3 studies included in this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
In an eventual Postmarketing Requirement, the applicant should provide clinical information from a 1-year (minimum) clinical study to support that there are no adverse effects on the corneal endothelium in 100 eyes (minimum) following the intravitreal administration of aflibercept.

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

Appendix 1

Product Quality Deficiencies

These include the deficiencies identified in the CDRH review as item #38. See Section 11 of this CDTL review regarding the incorrect assertions made in the CDRH review.

The following deficiencies were sent to Regeneron in a communication dated June 20, 2011. Regeneron submitted replies to these deficiencies in 3 amendments to the BLA; however, these were not reviewed during the first review cycle. Deficiencies that need to be addressed to support approval are copied here:

1. Regarding the cell banks:

(b) (4)

[redacted]

(b) (4)

2. As currently presented, it is not possible to assess the appropriateness of most of the in process controls (IPCs) identified in section 3.2.S.2.2.

a. Provide data to support the IPCs. For each IPC, historical data for each lot that was used for calculating mean should be presented; the IPC historical range, mean, and standard deviation (SD) should also be included.

b. For those IPC limits set using historical mean (b) (4) provide justification for setting IPC limits based on (b) (4)

(b) (4)

3. For DS process validation:

(b) (4)

(b) (4)

[redacted]

d. Regarding hold time:

i. Provide data supporting the hold time validation acceptance criteria.

ii. Submit results (raw data) from IEF testing for the samples that did not meet acceptance criteria for hold time validation.

(b) (4)

v. Table 13 in section 2.3.S.2 lists the completion status of processing hold times as "concurrent validation." Please clarify your intentions. Until validation of hold times is complete and data are submitted to the BLA, the hold times may not be considered part of the approved BLA process.

vi. For (b) (4) hold times, it is stated that microbial results met their acceptance criteria "demonstrating that the evaluated hold times are acceptable for this process" (section 3.2.S.2.5.7 p. 108). However, product quality assessment was included in the study design and testing is "currently in progress." Therefore, the hold time validations are not complete, and the hold times will not be acceptable as part of the approved BLA process.

vii. Regarding media hold times (Table 78, section 3.2.S.2.5.7, p. 109), bioburden acceptance criteria are presented; however, footnote "a" states that "a bioburden specification is not applicable." The media and media solution hold studies are performed to ensure that the hold times and conditions are appropriate with respect to the quality of the solutions for use in manufacture; bioburden is a critical parameter for media and solutions, and therefore should be included in these hold studies. Hold times should be based on materials prepared and stored as they would be for use in manufacturing. Therefore, the media and solutions should be filtered and stored under conditions comparable to those used during the manufacturing process, and appropriate bioburden criteria should be set and met. Provide appropriate media and solutions hold times and validation data to justify these times.

(b) (4)

(b) (4)

f. The section on Leachates from Contact Surfaces (3.2.S.2.5.9) does not provide any information on the assessments made for the components used and gives the impression that this assessment has not yet been done for the current process. Identify whether assessment of leachates for contact surfaces has been finalized and include the evaluation results for those products/steps requiring further evaluation based on your decision process.

g. Regarding the production-scale conformance batches:

i. Provide the validation protocols, including acceptance criteria.

ii. Provide the genealogy for all batches from C07003 through C07006. (b) (4)

iii. Provide data justifying the use (b) (4) outside of the historical average for those situations where (b) (4) was used.

iv. Provide all the validation data, including all operating parameters, performance values, and quality assessments. Include a column containing the historical ranges for each.

v. The action limits for operation and performance values were not discussed; identify any results that were outside the action limits that were identified in section 3.2.S.2.4.

vi. Regeneron's conclusion of the performance results for DS intermediate (section 3.2.S.2.5.11.1, p. 125) is that "in total, the outlying performance results comprised less than (b) (4) of the total results evaluated. These data suggests that the performance of the aflibercept manufacturing process is highly consistent." This statement is not supported by the information provided as this is not the total of the outlying performance results but is the performance results with particular results excluded. Two paragraphs earlier, it is stated that "in total, 123 of 2472 performance results (72 of 616 performance parameters) fell outside the (b) (4) standard deviation historical limits." Therefore, the actual outlying performance results comprised (b) (4) of the total results evaluated. No data were provided to allow an assessment of the results that were excluded by Regeneron. In your response to item g(iii), identify those datapoints that were excluded. For each of these datapoints, provide a justification for the validity of its exclusion.

vii. Clarify why there is a minimum load requirement for the (b) (4), (b) (4) (b) (4) (section 3.2.S.2.5.10.2, p. 133).

viii. Provide good quality reproductions of the IEF gels and individual band quantitation data for the conformance lots and any additional lots from which data will be used for setting specification acceptance criteria.

4. Regarding DS characterization:

a. Provide data for characterization of higher order (secondary/tertiary) structure in addition to the disulfide bonding assessment obtained using peptide mapping.

b. Regarding MALLS analyses:

i. Provide justification o (b) (4) l for performing an assessment to detect high molecular weight species. Include any data identifying if there are HMW species that are no longer detected (b) (4)

ii. Provide enlargements of the entire chromatograph (b) (4)

c. Regarding MS analysis:

i. Provide results from a blank run.

ii. Provide an enlarged view of the spectra surrounding the main aflibercept peaks and clarification of the "satellite" peaks/deconvolution artifacts.

(b) (4)

e. Provide relative percentage data for (b) (4) for each of the lots assessed.

f. Provide the complete integrated peak area analyses for (b) (4) (b) (4). In addition, there are unidentified peaks with percent areas that appear to be greater than (b) (4) based on the apparent size of (b) (4) identification of such peaks should have been determined. Submit data on all these peaks and the complete integrated peak area analysis to the BLA.

g. Provide the VEGF165 binding stoichiometry data for lot C08001M440.

h (b) (4) and (b) (4) should be assessed as process related impurities; there is no discussion of either of these cell culture components in either the validation section or the impurities section. Provide data regarding the amount present in drug substance or validate clearance of these process related impurities by the purification process.

(b) (4)

j. Regarding product size-related impurities:

i. It is stated in section 3.2.S.3.2.3.1.2 (p. 26) that all (b) (4) (including (b) (4) were "determined to possess the correct, predicted N-terminal sequence of aflibercept." However, Table 13 of that section states that the N-terminal sequence of (b) (4) was "not determined." Clarify this discrepancy.

ii. Table 13 lists only 3 N-terminal sequences for the non-reduced (b) (4) species (b) (4) while an additional sequence with truncation at (b) (4) is listed in

Table 12. It is not clear which species corresponds to the structure depicted for the (b) (4) species. Please clarify.

iii. Provide information regarding the locations of the truncations for species that initiate at the N-terminus.

iv. Provide to section 3.2.S.3.2.3.2 Table 14 the results for % aggregate for all lots, as these data should be available, and update the aggregation range to include the additional data.

(b) (4)

There appear to be HMW bands in the reduced SDS-PAGE gel shown in Figure 7 (section 3.2.S.3.2.3.1.2). However, in section 3.2.S.3.2.3.2 (p. 34), it is stated that "the lack of high molecular weight species in SDS-PAGE analysis suggests that aflibercept aggregates formed under stress conditions are reversible in SDS-PAGE and non-covalent in nature." It appears that there are discrepancies in the identification of the nature of the aflibercept aggregates; in addition, SDS-PAGE analyses of material stored under stress conditions are not described in this section. Clarify the apparent discrepancies and include data supporting the statements and conclusions made.

k. ISOQUANT analysis was used for the characterization of deamidation. Given that deamidation of asparagine can result in non-isomerized aspartate, and, therefore, that this assay would not monitor all potential deamidation reactions, provide information on non-isomerized forms of deamidated species that may be present.

5. Regarding specifications:

a. Provide justification for a proposed bioassay acceptance criterion of (b) (4), for DS intermediate, when the proposed acceptance criterion for DS is (b) (4)

b. Provide justification for a proposed charge heterogeneity acceptance criterion of (b) (4) for DS intermediate, when the proposed acceptance criterion for DS is (b) (4)

c. Provide justification for the proposed DS protein concentration acceptance criterion

(b) (4)

d. Describe and justify the use of stability data for setting proposed acceptance criteria for release (section 3.2.S.4.5.1). Include an assessment of how release at extremes that are supported by stability data would not allow for failure of aflibercept by the expiration timeline.

6. Regarding analytical procedures:

a. Clarify the statement that appearance and color and pH methods are "based on" USP and Ph. Eur. If different from the compendial method, provide information on the changes from compendia and the validation data where appropriate.

b. Provide data supporting the use of (b) (4) for the SEC assay that is intended to monitor levels of aggregate.

7. Provide batch analysis data for all DS intermediate lots and equivalent lots used as [redacted] (b) (4)

8. Regarding reference standard (RS):
   a. In section 3.2.S.5.1.2 Regeneron states that Qualification of future lots of reference standard will be performed using the commercial specifications. Please be aware that qualification of a RS based on the lot release acceptance criteria is not necessarily acceptable. Criteria must be in place to prevent drift in product quality. For example, assays that use RS as a comparator, such as the potency assay, would require a new RS to be very similar to the existing reference standard, and those requirements should be reflected in the protocol for qualification of a new RS. Please note that release of new RS would require submission of the protocol and data to the BLA for approval prior to use.
   b. Characterization results for the current RS lot [redacted] (b) (4) at qualification and data from earlier RS lots at the 24 month stability time point (section 3.2.S.5.1.3, Table 3) show that the molecular weights for HMW species and main species determined by SEC-MALLS were significantly lower for the 24 month stability samples than for the fresh qualification sample, indicating that there could have been an [redacted] (b) (4) change in each monomer during storage. Address the apparent instability of the RS under its storage condition of -80°C.

9. Regarding DS container closure:
   a. Regarding the microbial aerosol challenge (section 3.2.S.6.1.7.3), identify the manufacturing steps involving [redacted] (b) (4) and justify the use of [redacted] (b) (4) during container closure integrity testing. Clarify if step 18.3.2 of batch record document number MR1054, describing [redacted] (b) (4), is the same as the [redacted] (b) (4)
   b. Justify the use of the [redacted] (b) (4) leachable/extractable testing (section 3.2.S.6.1.4, Table 2).
   c. Clarify the calculation of [redacted] (b) (4) (3.2.S.6.1.4.2, p. 7), as the FTIR results listed in Table 4 are significantly higher than [redacted] (b) (4)
   d. Justify the methods used for concentration of samples from extractables testing, given that the concentration methods could lead to loss of some types of extractables.

10. Regarding DS stability:
    a. For SDS-PAGE and IEF testing, provide good quality reproductions of the gels containing the first and last available timepoints for all lots on stability.
    b. Provide freeze-thaw stability data for DS intermediate and DS. Alternatively, provide the controls that are in place to prevent thawed DS intermediate or DS from being refrozen and thawed again for use in future manufacturing.

11. Regarding post-approval stability protocol and stability commitment:
    a. Regeneron states in both section 3.2.S.7.2 and in the overall quality summary that one lot of drug substance will be [redacted] (b) (4) and that any failures will

be reported. As drug substance intermediate may be stored for an extended time, it should also [redacted] (b) (4) include all stability data for drug substance and drug substance intermediate in the AR.

b. We note that drug substance stability allows a [redacted] (b) (4) Identify the causes for this change in protein concentration. We also note that color and appearance are not tested to the same criteria at stability as at release. Please justify these differences.

12. Provide stability data for all formulated bulk lots tested. Include data for all timepoints available and provide good quality reproductions of SDS-PAGE and IEF gels for the first and last available timepoints for each of the lots.

13. Regeneron's formulation development studies to support upper and lower ranges and effect on product quality is ongoing. Very limited data were submitted to the BLA in section 3.2.P.2.1.4. Conclusions made based on these limited data need further justification:

a. Provide updated stability data and justification of conclusions made based on only 2 months of real time data. The submitted 1st and 2nd month timepoints for the "proven acceptable range" studies have no potency assessments for any of the completed portions of the study or for any available time point for the real time or accelerated portions of the study, no SDS-PAGE or IEF assessments for the real time or accelerated portions of the study, and no instron, imaged microscopy, FTIR assessments. Provide updated data to this section.

b. The studies for assessment of effects of [redacted] (b) (4) on product quality are not complete. Provide updated data to this section. In addition, provide justification for the filtering of data to exclude [redacted] (b) (4) [redacted] (b) (4)

c. Update the data from the studies assessing effects of [redacted] (b) (4) on product quality.

d. Update the data from the studies assessing the effects of manufacturing steps on product quality.

e. Regarding the assessment of effects of exposure to [redacted] (b) (4) on stability, section 3.2.P.2.2.1.7.3 states that the control was DP that was "not exposed to [redacted] (b) (4)" Clarify this statement; i.e. was DP manufactured without the use of [redacted] (b) (4) [redacted].

14. Regarding manufacturing process development:

a. On the subject of comparability:

i. The comparative stability study was not complete at the time of BLA submission. [redacted] (b) (4)

(b) (4) (b) (4) Regarding the decay profiles, as no primary data were provided, the degradation profile of individual aspects (e.g. the identity of HMW variants, LMW variants, charge variants that are generated) cannot be assessed; provide appropriate data to the BLA for review.

iii. Provide assessments of rates of degradation for the stressed (45°C) stability comparability studies based on statistical analyses.

iv. Provide data with respect to charge variants supporting the comparability of stability of DP in vials (b) (4) (b) (4) (b) (4)

(b) (4)

15. There are inconsistencies among the quality overall summary (2.3.I) Table 1, the manufacturer information in sections 2.3.P and 3.2.P, and the attachment to FDA Form 356h regarding manufacturers and the activities occurring at each manufacturing site. Update all of the sections to reflect the correct manufacturing and testing activities occurring at each site for each of the drug product presentations.

16. Regarding the description of the manufacturing process:

(b) (4)

17. Regarding controls of critical steps and intermediates:
    a. Submit formulated bulk stability data for all lots placed on stability. Include all time points available.
    b. In sections 3.2.P.3.4, it is not clear what type(s) of limit are associated with the given parameters and criteria. The limits are listed as action limits in section 3.2.P.3.3. Clarify and discuss the action taken. (b) (4)

(b) (4)

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20. According to the container closure section for (b) (4) vials (3.2.P.7 p.5), the secondary packaging contains one vial, one filtration needle, and one package insert; there is no mention of a syringe or delivery needle. Clarify the contents of the final packaging.

(b) (4)

22. Regarding the post approval stability commitment:
a. Include a requirement for reporting stability data from every lot put on stability protocols in the annual report.

(b) (4)

23. Regarding the adventitious agents safety evaluation:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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Appendix 2

Drug Product - Product Quality Microbiology Deficiencies

1. The shipping validation information indicates that due to the damage [redacted] (b) (4) [redacted] (b) (4) the blister pack design will be modified and the shipping validation studies will be repeated.

   [redacted] (b) (4)

[redacted] (b) (4)

f. [redacted] (b) (4)

4. Define the acceptable ranges for temperature, humidity, and chamber pressure for the [redacted] (b) (4)

5. Regarding the cycle development and process validation studies for [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4)

6. Provide the sensitivity of the bubble leak test for package integrity in terms of the breach size detectable.

[redacted] (b) (4)

8. Regarding container closure integrity testing of drug product in vials:

[redacted] (b) (4)

   b. Indicate whether container closure integrity has been validated for the [redacted] (b) (4) [redacted] (b) (4) vials using worst-case filling speed and crimping forces.
   c. Provide the bacterial concentration at the end of the [redacted] (b) (4) performed for the [redacted] (b) (4) and [redacted] (b) (4) vials.

[redacted] (b) (4)

[redacted] (b) (4)

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Product Quality Microbiology Possible PMCs (Drug Product)

1. Performance of the container closure integrity test in lieu of the sterility test for drug product stability samples at expiry is recommended.

[redacted] (b) (4)

3. Regarding hold time validation studies performed a[redacted] (b) (4) hold time studies for microbial control at scale is facility-specific and should be performed for each facility even if the processes are the same and identical equipment is used. Provide at scale end of hold bioburden and endotoxin data from three lots of drug product manufactured at the [redacted] (b) (4) vial site and from one additional lot of drug product manufactured at the [redacted] (b) (4) syringe site.

Product Quality Microbiology Clarification Questions (Drug Product)

1. Indicate whether the endotoxin release testing of the finished drug product will employ a 1:8 dilution or other dilution below the MVD.

2. A discrepancy is noted in the BLA for [redacted] (b) (4) vial manufacturing [redacted] (b) (4) (b) (4)

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Signatures:

Reviewer Signature _____ 8/12/11
William Boyd, MD

Supervisor Signature _____ MD 8/12/11 Concurrence Yes X No ___
Wiley Chambers, M.D.

CLINICAL REVIEW

Application Type	BLA
Submission Number	125-387
Submission Code	000
Letter Date	2/17/11
Stamp Date	2/18/11
PDUFA Goal Date	8/18/11
Reviewer Name	Sonal D. Wadhwa, MD
Review Completion Date	7/8/11
Established Name	aflibercept injection
(Proposed) Trade Name	Eylea
Therapeutic Class	anti-VEGF
Applicant	Regeneron
Priority Designation	P
Formulation	Intravitreal injection
Dosing Regimen	Intravitreal injection
Indication	Treatment of patients with Neovascular (wet) AMD
Intended Population	Patients with wet AMD

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

BLA 125-387 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of aflibercept injection for the treatment of neovascular AMD.

1.2 Risk Benefit Assessment

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Post-marketing Risk Management Activities

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

1.4 Recommendations for other Post-marketing Study Commitments

The applicant should provide clinical information from a 1-year (minimum) clinical study to support that there are no adverse effects on the corneal endothelium following the intravitreal administration of aflibercept.

2 Introduction and Regulatory Background

2.1 Product Information

VEGF Trap (aflibercept) is a recombinant protein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to an IgG1 Fc. VEGF Trap is a specific antagonist that binds and inactivates circulating VEGF and PlGF (placental growth factor 1) in the blood stream and in the extravascular space. In comparison, pegaptanib (Macugen) is an inhibitor of the VEGF165 isomer and ranibizumab (Lucentis) and bevacizumab (Avastin), are inhibitors of all VEGF-A isomers. Therefore, VEGF Trap not only inhibits all isoforms of VEGF-A, but also inhibits PlGF.

2.2 Tables of Currently Available Treatments for Proposed Indications

NDA/BLA	Drug	Approval	Indication
NDA 21-119	Photodynamic therapy (PDT)/ Verteporfin	April 2000	Indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to AMD, pathologic

			myopia, or POHS.
NDA 21-756	Macugen (pegaptanib injection)	December 2004	Indicated for the treatment of neovascular (wet) age-related macular degeneration
BLA 125-156	Lucentis (ranibizumab injection)	June 2006	Indicated for the treatment of patients with neovascular (wet) age-related macular degeneration

In addition to the products above, focal laser therapy has been used to close abnormal leaking vessels secondary to AMD, however rarely used currently since the approval of the above drugs.

2.3 Availability of Proposed Active Ingredient in the United States

Aflibercept is not an approved product in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

There have been no additional safety concerns raised with this class of therapeutic products other than those discussed within this review.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

IND 12,462 for VEGF Trap-Eye for the treatment of wet AMD was opened on June 15, 2005.

A No-Agreement letter was sent to Regeneron on March 5, 2007, regarding their January 18, 2007, SPA request for the Phase 3 Study VGFT-OD-0605. A second No-Agreement letter was sent to Regeneron on July 13, 2007, regarding their May 31, 2007, SPA amendment for the Phase 3 Study VGFT-OD-0605.

On September 8, 2010, a preBLA Clinical meeting was held to discuss clinical, clinical pharmacology, statistical, and regulatory issues concerning the upcoming BLA submission for treatment of AMD

On June 17, 2011, the FDA Dermatologic and Ophthalmic Drug Advisory Committee reviewed BLA 125387. The committee unanimously agreed (all 10 voting members) that adequate safety and efficacy for aflibercept injection had been demonstrated for the treatment of neovascular age-related macular degeneration.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI was consulted for this study. DSI inspected 3 sites. The inspections of Dr. Abraham, Dr. Heier, and Dr. Micheals found no problems with the data.

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trial was not conducted in compliance with good clinical practices. Regeneron certifies that it did not use the services of any person debarred. Seth Yoser was selected as an investigator for the VGFT-OD-0605 study. He screened 1 patient on 1/22/08 but no patient from his site was randomized and included in the study. No patients were treated by Seth Yoser for the study. His site was terminated and closed by Regeneron on 6/20/08. He was debarred by FDA effective date 5/20/10 with Federal register date 8/18/10.

3.3 Financial Disclosures

Financial disclosure forms were reviewed. The following investigators revealed they had financial disclosures.

Name	Role	Study	Financial Disclosure
A. Ho, MD	PI	View #1	(b) (6) in payment
(b) (6)			(b) (6) (b) (6)
J. Heier, MD	PI	View #1	(b) (6) n payment and involved in aflibercept steering committee
(b) (6)			
Q. Nguyen, MD	PI	View #1	Involved in aflibercept steering committee and d/c from study in 2009
(b) (6)			
(b) (6)			(b) (6)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Drug Product Formulation Used in Clinical Trials

Component	Formulation Composition	
	ITV-1	ITV-2
Aflibercept	5, 10, 20, 40 mg/mL	10 and 40 mg/mL
Sodium phosphate (b) (4) (b) (4)	(b) (4)	
Sodium phosphate, (b) (4) (b) (4)		
Sodium chloride		
Sucrose		
Polysorbate 20		

(b) (4)

(b) (4)

Vials
For some earlier trials both ITV-1 and ITV-2 formulations were used. Vials with ITV-2 were used in both VIEW #1 and VIEW #2. The volume of injection is 50 µl (0.05 mL) for the 0.5 mg dose of VEGF Trap-Eye and the 2 mg dose of VEGF Trap-Eye. The study drug is withdrawn using aseptic technique through a filter needle attached to a 1 mL syringe. The needle is to be aseptically removed from the syringe and replaced with a 30 gauge needle for the intravitreal injection.

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Aflibercept is a anti-VEGF recombinant antibody. It is a specific antagonist that binds and inactivates circulating VEGF and PlGF in the blood stream and in the extravascular space.

4.4.2 PK/PD

In patients with neovascular AMD, following intravitreal administration of aflibercept ophthalmic solution, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept:VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (ie. aflibercept:VEGF complex).

Absorption/Distribution
Following intravitreal administration of 2 mg per eye of aflibercept ophthalmic solution (Study VGFT-OD-0702.PK) to patients with AMD, the mean plasma Cmax of free aflibercept was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL) and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable 2 weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeat doses intravitreally every 4 weeks. The volume of distribution of free aflibercept following intravenous administration of aflibercept has been determined to be approximately 6 L. The aflibercept:VEGFcomplex plasma concentrations reach Cmax in 14 to 28 days following a 2- mg intravitreal administration with a mean plasma Cmax of approximately 0.186 mcg/mL (range from 0.100 to 0.286 mcg/mL).

Metabolism/Elimination
Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after IV administration of doses of 2 to 4 mg/kg aflibercept.

The exploratory subgroup analyses in Phase 3 study VIEW2 did not reveal any clinically relevant influence of the co-variants including age, sex, BMI, renal function (determined as creatinine clearance), or geographic region (Europe vs. Japan) on the plasma concentrations of free aflibercept or aflibercept :VEGF complex.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Study	Phase	Study Design	Objective	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Status
VGFT-OD-0603	1	Double-masked, randomized with open-label expansion cohort	Study designed to assess the safety and tolerability of 2 formulations of VEGF Trap-Eye (IVT-1 and IVT-2). Studied the following for 12 weeks: • 4mg Q4 IVT-1 • 4mg Q4 IVT-2 • 4mg Q4 open label IVT-2 After 12 weeks patients received 4mg prn.	20	AMD	12 weeks	Completed
VGFT-OD-0502	1	Part A-Phase 1, open-label dose escalation Part B-Randomized, double-masked, active controlled Part C-Randomized, double-masked	The first study in which VEGF Trap-Eye was IVT administered to subjects with AMD. This study comprised 3 single-dose sub-studies (parts A, B, and C) and enrolled a total of 51 subjects. Each of the single-dose periods in parts A, B, and C was followed by a treatment-free, extended follow-up period lasting up to 1 year. Studied doses of aflibercept ranging from 0.05mg-4mg.	51	AMD	57 days (primary analysis) and continued up to 12 months	Completed
VGFT-OD-0702	Extension Phase 1/2	Single masked, randomized to compare pre-filled syringe (PFS) vs. vial	Subjects who completed VGFT-OD-0508, VGFT-OD-0603, or VGFT-OD-0502 were given the opportunity to enroll in this long-term extension study. This is an ongoing study designed to provide long-term safety information (beyond 1 year) on the use of VEGF Trap-Eye 2 mg,	157	AMD	38 months	Active but not recruiting.

Study	Phase	Study Design	Objective	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Status
			administered on an as needed (prn) basis. It also provides comparative safety information for 2 delivery modes of VEGF Trap-Eye: vials (as administered to subjects in the phase 3 pivotal trials) and pre-filled syringes (PFS). VEGF Trap-Eye 2mg prn (PFS)-99 patients VEGF Trap-Eye 2mg prn (vials)-50 patients				
VGFT-OD-0508 (CLEAR-IT AMD-2)	Phase 2 dose ranging	Randomized, double-masked	Obtain safety and efficacy data for 5 parallel dosing groups of VEGF Trap-Eye: • 0.5 mg q12 weeks (32 patients) • 0.5 mg q4 weeks for 12 weeks (32 patients) • 2.0 mg q12 weeks (31 patients) • 2.0 mg q4 weeks for 12 weeks (31 patients) • 4.0 mg q12 weeks (31 patients) Beginning at Week 16, subjects in all treatment arms were evaluated every 4 weeks for subsequent PRN dosing at the randomized dose level.	159	AMD	12 weeks (primary endpoint) continued to 52 weeks	Completed
VIEW #1 (VGFT-OD-0605)	Phase 3	Double-masked, randomized, active controlled	Designed to obtain safety and efficacy data for four parallel treatment groups: Ranibizumab q4 weeks (306 patients) VEGF Trap-Eye 2.0 mg q4 weeks (304 patients) VEGF Trap-Eye 0.5 mg q4 weeks (304 patients) VEGF Trap-Eye 2.0 mg q8 weeks (313 patients)	1217	AMD	52 weeks (primary endpoint) continued to 96 weeks	Ongoing, 52 weeks complete for all patients
VGFT-OD-0910	Phase 3 extension of VIEW 1	Open label	Long term safety and tolerability 2mg capped prn (at least every 12 weeks)	178 (as of 9/15/10). Target is 960 patients.	AMD	18 months	Ongoing

Aflibercept has also been studied in patients with DME, CRVO, and oncology indications. The main support for safety and efficacy for the AMD indication comes from the following trials: VIEW #1, VIEW #2, and VGFT-OD-0702 and will therefore be the focus of this review.

5.2 Review Strategy

The sources of clinical data utilized in this review include the studies listed in section 5.1.

5.3 Discussion of Individual Studies

VIEW #1

Study VGFT-OD-0605: "A Randomized, Double-Masked Active Controlled Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap-Eye in Subjects With Neovascular AMD"

Short Title: VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1)

Primary Objective: The primary objective of this study is to assess the efficacy of intravitreally administered of VEGF Trap-Eye compared to ranibizumab (in a non-inferiority paradigm) in preventing moderate vision loss in subjects with all sub-types of neovascular AMD.

This is an ongoing randomized, double-masked, active controlled, multi-center, phase 3 study conducted in the US and Canada. The study consists of a 21-day screening period followed by clinic visits and IVT injections of study drug administered every 4 or 8 weeks (including sham injections at interim study visits when study drug was not administered) for 52 weeks (total of 16 visits) during the first year of the study. No sham injections were given at week 52. The entire study duration is approximately 2 years (96 weeks plus the recruitment period). During the second year of treatment, subjects will be evaluated every 4 weeks and will receive IVT injections of study drug at intervals determined by specific dosing criteria, but at least every 12 weeks. During the second year of treatment, sham injections will not be given. During this period, injections may be given as frequently as every 4 weeks, but no less frequently than every 12 weeks, according to specific pre-specified re-dosing criteria. The pre-specified criteria are:

- Increase in central retinal thickness >=100 microns compared to lowest previous value as measured by OCT
- A loss from the best previous letter score of >=5 ETDRS letter in conjunction with recurrent fluid as indicated by OCT
- New or persistent fluid as indicated by OCT
- New onset classic neovascularization
- New or persistent leak on FA
- New macular hemorrhage
- 12 weeks has elapsed since the previous injection

The results are based on the data obtained between start of enrollment and the data cut-off point for each individual subject at the week 52 visit when the primary endpoints of this study were obtained. The period covered in the first 52 weeks for VIEW #1 is 8/2/07 (first subject's first dose) to 9/14/10 (last subject's last visit for the primary endpoint) for year 1. The study is

currently ongoing for the second year as planned while masking is maintained for subjects and personnel involved in the study.

On day 1, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

1. 2 mg VEGF Trap-Eye administered every 4 weeks (2Q4)
2. 0.5 mg VEGF Trap-Eye administered every 4 weeks (0.5Q4)
3. 2 mg VEGF Trap-Eye administered every 8 weeks (2Q8) plus a sham injection at interim 4-week visits (when study drug was not administered), following 3 initial monthly doses
4. 0.5 mg ranibizumab administered every 4 weeks (RQ4)

Inclusion Criteria:

1. Signed informed consent
2. Men and women ≥ 50 years of age
3. 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
4. CNV must be at least 50% of total lesion size
5. ETDRS BCVA of: 20/40-20/320 in the study eye
6. Willing, committed, and able to return for all clinic visits and completed all study-related procedures
7. Understand and willing to sign the ICF

Exclusion Criteria:

1. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins
3. Prior treatment with anti-VEGF agents as follows:
    a. Prior treatment with anti-VEGF therapy in the study eye was not allowed
    b. Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not FDA approved, ie. bevacizumab) was allowed up to 3 months prior to first dose in the study, and such treatments were not allowed during the study. Prior treatment with an FDA/Health Canada approved anti-VEGF therapy in the fellow eye was allowed.
    c. Prior systemic anti-VEGF therapy, investigational or FDA/Health Canada approved was only allowed up to 3 months prior to first dose, and was not allowed during the study.
4. Total lesion size > 12 disc areas (DAs) (30.5 squared mm, including blood, scars and neovascularization) as assessed by FA in the study eye
5. Subretinal hemorrhage that was either 50% or more of the total lesion area, or if the blood was under the fovea and was 1 or more DAs in size in the study eye (if the blood was under the fovea, then the fovea must have been surrounded 270 degrees by visible CNV).
6. Scar or fibrosis, making up > 50% of total lesion in the study eye
7. Scar, fibrosis, or atrophy involving the center of the fovea

8. Presence of RPE tears or rips involving the macula in the study eye
9. History of any vitreous hemorrhage within 4 weeks prior to visit 1 in the study eye
10. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of 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.
11. 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
12. Prior vitrectomy in the study eye
13. History of retinal detachment or treatment or surgery for retinal detachment in the study eye
14. Any history of macular hole of stage 2 and above in the study eye
15. Any intraocular or periocular surgery within 3 months of day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as it was unlikely to interfere with the injection
16. Prior trabeculectomy or other filtration surgery in the study eye
17. Uncontrolled glaucoma (defined as IOP ≥25 mmHg despite treatment with anti-glaucoma medication) in the study eye
18. Active intraocular inflammation in either eye
19. Active ocular or periocular infection in either eye
20. Any ocular or periocular infection within the last 2 weeks prior to screening in either eye
21. Any history of uveitis in either eye
22. Active scleritis or episcleritis in either eye
23. Presence or history of scleromalacia in either eye
24. Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of an YAG posterior capsulotomy) in the study eye
25. Previous therapeutic radiation in the region of the study eye
26. History of corneal transplant or corneal dystrophy in the study eye
27. Significant media opacities, including cataract, in the study eye which might interfere with VA, assessment of safety, or fundus photography
28. Any concurrent intraocular condition in the study eye (ie. cataract) that, in the opinion of the investigator, could have required either medical or surgical intervention during the 96 week study period
29. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could have either increased the risk to the subject beyond what was to be expected from standard procedures of intraocular injection, or which otherwise may have interfered with the injection procedure or with evaluation of efficacy or safety
30. 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
31. Participation as a subject in any clinical study within the 12 weeks prior to day 1
32. Any systemic or ocular treatment with an investigational agent in the past 3 months prior to Day 1

33. The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to Day 1.
34. Any history of allergy to povidone iodine
35. Known serious allergy to the fluorescein sodium for injection in angiography
36. Presence of any contraindications indicated in the FDA approved label for ranibizumab
37. Females who were pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study. Adequate contraceptive measures included oral contraceptives (stable use for 2 or more menstrual cycles prior to screening); IUD; Depo-Provera; Norplant System implants; bilateral tubal ligation; vasectomy; condom or diaphragm plus either contraceptive sponge, foam or jelly

VEGF Trap-Eye was supplied by Regeneron Pharmaceuticals, Inc. and was administered by IVT injection using standard ophthalmic techniques. See section 4.1 for detail. Sham injections for the 2Q8 group were performed using a syringe without a needle with no active drug and without intraocular penetration. All VEGF Trap-Eye study medication and sham treatments were packaged in identical packaging with identical labeling, except for the kit number. An unmasked investigator performed the study drug or sham injection. The unmasked investigator was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments at 30 to 60 minutes post-IVT-injection. A separate masked physician assessed AEs and supervised the masked assessment of efficacy. All other study site personnel were required to remain masked to treatment assignment in order to allow for an unbiased assessment of VA, safety, and ancillary study measures.

Treatment failure during the first 52 weeks of the study was defined as a decrease from baseline in BCVA by 15 or more letters at 2 consecutive assessments, 4 weeks apart. A subject who qualified as a treatment failure could be, but was not required to be, discontinued from the study. If a subject did withdraw, he or she was required to complete the year 2 end-of study/early termination visit procedures.

Roles	Primary Responsibility
Principal Investigator	• Oversee entire conduct of study • Responsible for all aspects of study conduct.
Masked Investigator	• May perform screening assessments • Evaluates vital signs, performs physical exams • Performs ophthalmic exams at all study visits (except immediately post IVT injection) • Evaluates all safety, including review of images for safety concerns at the site • Responsible in year 2 to assess the need for treatment at each study visit according to protocol criteria • Contact with sponsor regarding medical information not relegated to study coordinator
Unmasked Investigator	• May perform screening assessments • Injection of Study Drug • Assess Safety at 30-60 minute post IVT exam
Unmasked Investigator or their unmasked designee	• Receives Study Drug • Preparation of study drug for injection • Ranibizumab supply reconciliation and reimbursement • Study Drug Destruction
Masked VA Examiner	• Refraction and BCVA Testing
Photographer/FA Technician/OCT Technician	• Collect OCT images, fundus photographs and angiographic images • Assure transfer of images to reading centers where required • Assure proper archiving of images
Study Coordinator	• Primary responsibility for administrative and logistical aspects of study conduct • Primary point of contact with CRO and sponsor for all non-medical matters

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ON ORIGINAL

List of Investigators: VGFT-OD-0605 (VIEW# 1)

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(194) Allen County Retinal Surgeons	7900 West Jefferson, Suite 300 Fort Wayne, IN 46804 (260) 436-2181	Matthew E. Farber, MD	10
(104) Allegheny General Hospital	420 E. North Avenue, Suite 116 Pittsburgh, PA 15212 (412) 359-6300	Thierry Verstraeten, MD	6
(323) Associates in Ophthalmology, Ltd.	9970 Mountain View Drive, 2nd Floor West Mifflin, PA 15122 (412) 653-3080	Miguel A. Busquets, MD	4
(170) Associated Retina Consultants	7600 North 15th Street, Suite 155 Phoenix, AZ 85020 (602) 242-4928 x170	Clive Sell, MD	15
(239) Associated Retina Consultants PC	3535 W.Thirteen Mile Road, Suite 348 Royal Oak, MI 48073 (248) 288-9132	Tarek S. Hassan, MD	1
(106) Austin Retina Associates	801 West 38th Street, Suite 200 Austin, TX 78705 (512) 451-0103	James, Dooner, MD	6
(142) Black Hills Regional Eye Institute	2800 3rd Street Rapid City, SD 57701 (605) 341-9190	Prema Abraham, MD	23
(191) Barnes Retina Institute	4921 Parkview Place, Suite 12B St. Louis, MO 63110 (314) 367-1181	Gaurav Shah, MD	4
(197) Beth Israel Deaconess Medical Center	330 Brookline Avenue, 5th Floor Boston, MA 02215 (617) 667-3391	Jorge Arroyo, MD	1
(504) Canadian Centre for Advanced Eye Therapeutics	1880 Sismet Road Mississauga, Ontario L4W 1W9 Canada (905) 212-9482	Fareed Ali, MD	3
(152) Center for Retina & Macular Disease	250 Avenue K Southwest, Suite 200 Winter Haven, FL 33880 (863) 297-5400	Michael Tolentino, MD	29
(130) Cumberland Valley Retina Consultants PC	1150 Opal Court Hagerstown, MD 21740 (301) 665-1712	John Wroblewski, MD	17
(508) Calgary Retina Consultants	200-5340 1 Street Southwest Calgary, Alberta T2H0C8 Canada (403) 286-6802 x117	Amin Kherani, MD	7
(261) Capital Region Retina, PLLC	1365 Washington Avenue, Suite 101 Albany, NY 12206 (518) 437-1111	Jeffrey Stern, MD	1
(125) Carolina Retina Center, PA	7620 Trenholm Road Columbia, SC 29223 (803) 736-7200	Jeffrey G. Gross, MD	3

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(132) Central Florida Retina	44 Lake Beauty Drive, Suite 300 Orlando, FL 32806 (720) 848-2500	John Olson, MD	4
(175) Charlotte Eye, Ear, Nose & Throat Associates, PA	6035 Fairview Road Charlotte, NC 28210 (704) 295-3182	David Browning, MD	4
(121) Cincinnati Eye Institute	1945 CEI Drive Cincinnati, OH 45242 (513) 984-5133	Michael Petersen, MD	8
(308) The Cleveland Clinic Foundation	9500 Euclid Avenue Cleveland, OH 44195 (216) 444-6702	Peter K. Kaiser, MD	5
(233) Colorado Retina Associates	2005 Franklin Street, Suite 180 Denver, CO 80205 (303) 831-7419	Curtis Hagedorn, MD	9
(307) Harkness Eye Institute at Columbia University	635 West 165th Street, Room 111 New York, NY 10032 (212) 305-5922	Stanley Chang, MD	3
(108) Connecticut Retina Consultants LLC	4920 Main Street, Suite 309 Bridgeport, CT 06606 (203) 365-6565	Philip Falcone, MD	3
(283) Davis Duehr Dean Health Systems	1025 Regent Street Madison, WI 53715 (608) 282-2143	Stephen Sramek, MD	2
(120) Delaware Valley Retina Associates	4 Princess Road, Suite 101 Lawrenceville, NJ 08648 (609) 896-1414	Jeffrey Lipkowitz, MD	1
(501) Associated Consulting Ophthalmologists, Dalhousie University	1278 Tower Road Halifax, Nova Scotia B3H 2Y9, Canada (902) 473-3947	John D. Dickinson, MD	9
(109) East Bay Retina Consultants Inc.	3300 Telegraph Avenue Oakland, CA 94609 (510) 444-1600	Eugene Lit, MD	13
(303) East Florida Eye Institute	509 Southeast Riverside Drive Suite 302 Stuart, FL 34994 (772) 287-9000	Ronald E. Frenkel, MD	9
(340) East Texas Eye Care Associates	2440 East 5th Street Tyler, TX 75701 (903) 595-0500	Thomas W. Bochow, MD	2
(306) North Shore University Health System Research Institute	2425 West 22nd Street, Suite 207 Oak Brook, IL 60523 (847) 657-1750	Aaron Weinberg, MD	2
(276) Eye Associates of New Mexico	806 Dr Martin Luther King Boulevard Albuquerque, NM 87106 (505) 842-6575	Mark Chiu, MD	2

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(187) Eye Care Specialists	703 Rutter Avenue Kingston, PA 18704 (570) 288-7405	Erik Kruger, MD	10
(101) Eye Centers of Louisville	4010 Dupont Circle, Suite 380 Louisville, KY 40207 (502) 214-3399	Steven Bloom, MD	6
(348) Eye Medical Center of Fresno	1360 East Herndon, Suite 301 Fresno, CA 93720 (559) 449-5060	George A. Bertolucci, MD	2
(185) Eye Specialists of Louisville Department of Ophthalmology	301 E. Muhammad Ali Blvd., Suite 419A Louisville, KY 40202 (502) 852-7387	Tongalp Tezel, MD	4
(227) Eye Surgical Associates	1710 South 70th Street Lincoln, NE 68506 (402) 421-3039	Matthew Wood, MD	15
(339) Eyesight Ophthalmic Services	155 Borthwick Avenue, Suite 200 Portsmouth, NH 03801 (603) 436-1773	Richard Chace, MD	3
(223) Fletcher Allen Health Care	199 Main Street, 2nd Floor Burlington, VT 05401 (802) 847-4520	Brian Kim, MD	3
(124) Florida Eye Clinic	160 Boston Ave Altamonte Springs, FL 32701 (407) 834-7776	Robert Feldman, MD	12
(103) Florida Eye	1717 Woolbright Road Boynton Beach, FL 33426 (561) 737-5500	Randy S. Katz, MD	4
(251) Foresight Studies, LLC	9623 Huebner Road, Suite 100 San Antonio, TX 78240 (210) 615-6565	David Scales, MD	5
(503) Hospital Maisonneure Rosemont Montreal University	5415 Boul l'Assumption CSA RC Aile F Porte 133 Montreal Quebec H1T 2M4, Canada (514) 252-3400	Pierre Labelle, MD	4
(168) Indiana University Retina Service	702 Rotary Circle, Room 2338 Indianapolis, IN 46202 (317) 278-3322	Hua Gao, MD	2
(502) Ivey Eye Institute	268 Grosvernor Street London, Ontario N6A 4V2 Canada (519) 685-8500	John R. Gonder, MD	13
(210) John Kenyon American Eye Institute	519 State Street New Albany, IN 47150 (812) 948-0616	Howard Lazarus, MD	16
(237) Joseph R Podhorzer MD PLLC	445 Kings Highway, 1st Floor Brooklyn, NY 11223 (718) 645-2201	Joseph Podhorzer, MD	2

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(266) Kaiser Permanente Northwest	3600 N. Interstate Avenue Portland, OR 97227 (503) 331-6467	Anthony Cirino, MD	5
(234) Kaiser Permanente	22550 E. Savi Ranch Parkway Yorba Linda, CA 92887 (714) 685-3639	Suri Appa, MD	4
(293) Lahey Clinic MCNS.	1 Essex Center Drive Peabody, MA 01960 (978) 538-4412	Gregory Blaha, MD	5
(179) Loma Linda University	11370 Anderson Street, Suite 1800 Loma Linda, CA 92354 (909) 558-2170	Joseph Fan, MD	13
(336) MaculaCare, PLLC	52 East 72nd Street New York, NY 10021 (212) 439-9600	Daniel Rosberger, MD	1
(113) Magruder Eye Institute	1911 North Mills Ave Orlando, FL 32803 (407) 893-8200 x8231	Nader Moinfar, MD	3
(140) Maine Eye Center	15 Lowell Street, Retina Department Portland, ME 04102 (207) 523-5368	Jeffrey Moore, MD	5
(247) Maine Vitreoretinal Consultants LLC PA	12 Stillwater Avenue Bangor, ME 04401 (207) 945-4474	Deborah S. Hoffert, MD	2
(225) Mayo Clinic - Rochester	200 First Street Southwest Rochester, MN 55905 (507) 284-3726	Sophie J. Bakri, MD	8
(332) Med Eye Associates	5950 Sunset Drive Miami, FL 33143 (305) 733-1281	Zachary K. Segal, MD	13
(296) Medical Center Ophthalmology Associates	9157 Huebner Road San Antonio, TX 78240 (210) 697-2020	Michael A. Singer, MD	4
(169) Medical College Of Wisconsin Eye Institute	925 North 87th Street Eye Institute, 4th Floor Milwaukee, WI 53226 (414) 456-7868	David V. Weinberg, MD	15
(279) Mid-Atlantic Retina	840 Walnut Street, Suite 1020 Retina Service Philadelphia, PA 19107 (610) 649-1970	Joseph I. Maguire, MD	12
(102) Midwest Eye Insititute	201 Pennsylvania Parkway Indianapolis, IN 46280 (317) 817-1822	Thomas Ciulla, MD	16
(236) Northern California Retina - Vitreous Associates	2485 Hospital Drive, Suite 200 Mountain View, CA 94040 (650) 988-7480	James Palmer, MD	10

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(162) New York Eye & Ear Infirmary	310 East 14th Street South Building, Suite 319 New York, NY 10003 (212) 979-4251	Richard Rosen, MD	2
(153) National Ophthalmic Research Institute	6901 International Center Boulevard Fort Myers, FL 33912 (239) 938-1284	Joseph P. Walker, MD	9
(117) New England Retina Associates	400 Bayonet Street, Suite 206 New London, CT 06320 (860) 444-1292	Nauman Chaudhry, MD	14
(209) Ocala Eye	3130 SW 32nd Ave Ocala, FL 34474 (352) 291-5210	Chander Samy, MD	4
(176) Ochsner Clinic Foundation	1514 Jefferson Highway New Orleans, LA 70121 (504) 842-3952	Laurence Arend, MD	1
(151) Ophthalmic Consultants of Long Island	360 Merrick Road, 3rd Floor Lynbrook, NY 11563 (516) 593-4026 x251	Glenn Stoller, MD	5
(146) Ophthalmic Consultants of Boston	50 Staniford Street, Suite 600 Boston, MA 02114 (617) 314-2694	Jeffrey S. Heier, MD	32
(148) Ophthalmology Associates	1201 Summit Avenue Fort Worth, TX 76102-4427 (817) 332-2020	John Parchue, MD	14
(242) Orange County Retina Medical Group	1200 North Tustin Avenue, Suite 140 Santa Ana, CA 92705 (714) 972-8432	Sanford Chen, MD	10
(180) Paducah Retinal Center	1900 Broadway Street, Suite 2 Paducah, KY 42001 (270) 443-4393	Carl W. Baker, MD	2
(145) Palmetto Retina Center, LLC	124 Sunset Court West Columbia, SC 29169 (803) 931-0077	W. L. Clark, MD	22
(510) The Medical Center Pasqua Hospital	1-4101 Dewdney Avenue Regina, Saskatchewan S4TA5, Canada (306) 766-2333	Raul Garcia, MD	8
(195) Premier Retina Specialists	840 Central Drive Odessa, TX 79761 (432) 332-2682	Richard Culbert, MD	3
(114) Retina Care Specialists LLP	3399 PGA Boulevard, Suite 220 Palm Beach Gardens, FL 33410 (561) 624-0099	Mark Michels, MD	13
(196) Rocky Mountain Retina	4400 South 700 East, Suite 200 Salt Lake City, UT 84107	David W. Faber, MD	12

APPEARS THIS WAY ON ORIGINAL

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
Consultants	(801) 264-4444	David H. Ren, MD	1
(252) Regional Retina	7330 Fern Avenue, Suite 702 Shreveport, LA 71105 (318) 798-6699	David A. Glaser, MD	5
(274) Retina Associates of St. Louis, Inc.	1224 Graham Road, Suite 3011 Florissant, MO 63031 (314) 839-1211	Ernest Guillet, MD	11
(165) Retina Associates of Western New York	160 Sawgrass Drive, Suite 200 Rochester, NY 14620 (585) 442-3411	Kenneth Wald, MD	3
(311) Retina Associates of New York	140 East 80th Street New York, NY 10021 (212) 772-0600	Kenneth Diddie, MD	3
(301) Retinal Consultants of Southern California	1250 La Venta Drive, Suite 208 Westlake, CA 91361 (805) 379-0200	Michael Antworth, MD	13
(220) Retina Consultants of Carolina	1126 Grove Road Greenville, SC 29605 (864) 233-5722	Darrin Levin, MD	1
(123) Retina Consultants of Michigan	29201 Telegraph Road, Suite 606 Southfield, MI 48034 (248) 356-8610	Sean Adrean, MD	3
(284) Retina Consultants of Orange County	301 West Bastanchury Road, Suite 285 Fullerton, CA 92835 (714) 738-4620	James K. Luu, MD	8
(346) Retina Consultants of Southern Colorado P.C.	3030 North Circle, Suite 301 Colorado Springs, CO 80909 (719) 331-7835	John O. Mason, III, MD	4
(137) Retina Consultants of Alabama	700 South 18th Street, Suite 707 Birmingham, AL 35223 (205) 918-0047	Murray J. Erasmus, CHB, MB	39
(505) Retina Consultants of Victoria	212-911 Yates Street Victoria, British Columbia V8V 1B3, Canada (250) 598-1252	Pravin U. Dugel., MD	5
(183) Retinal Consultants of Arizona	1101 E. Missouri Avenue Phoenix, AZ 85014 (602) 222-2221	Richard Garfinkel, MD	5
(314) Retina Group of Washington	8505 Arlington Boulevard, Suite 300 Fairfax, VA 22031 (703) 698-9335	Alexander Eaton, MD	27
(224) Retina Health Center	1567 Hayley Lane, Suite 101 Fort Myers, FL 33907 (239) 337-3337 x220	Tom Chang, MD	8
(157) Retina Institute of California	301 W. Huntington Drive, Suite 107 Arcadia, CA 91007 (626) 568-8838		

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(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(202) Retina Research Institute of Texas	5441 Health Center Drive Abilene, TX 79606 (325) 690-4414	Sunil Patel, MD	1
(273) Retina Specialists of Alabama LLC	1201 11th Avenue South, Suite 300 Birmingham, AL 35205 (205) 933-2625	Robert Morris, MD	4
(334) Retina Vitreous Surgeons of CNY, PC	3107 East Genesee Street Syracuse, NY 13224 (315) 445-8166	G. R. Hampton, MD	6
(144) Retina-Vitreous Associates	8641 Wilshire Boulevard, Suite 210 Beverly Hills, CA 90211 (310) 289-2478	David Boyer, MD	23
(258) Retinal & Ophthalmic Consultants PC	1500 Tilton Road Northfield, NJ 08225 (609) 646-5200	Thomas Margolis, MD	9
(119) Retina Associates S.W., P.C.	6561 East Carondelet Drive Tucson, AZ 85710 (520) 886-2597	April Harris, MD	4
(240) Retina Associates PC	4414 Lake Boone Trail, Suite 302 Raleigh, NC 27607 (919) 782-8038	John Denny, MD	14
(135) Retina Associates	3525 Prytania Street, Suite 320 New Orleans, LA 70115 (504) 895-3961	Kurt A. Gitter, MD	2
(299) Johns Hopkins Hospital School of Medicine Wilmer Eye Institute	600 North Wolfe Street Maumenee 721 Baltimore, MD 21287 USA (410) 502-5383	Quan D. Nguyen MD	6
(190) Retina Care Center	6115 Falls Road, Suite 300 Baltimore, MD 21209 (410) 377-7611	Eric Suan, MD	9
(305) Retina Center PC	6585 N. Oracle Road Tucson, AZ 85704 (520) 742-7444	Henry Hudson, MD	5
(214) Retina Center	710 East 24th Street, Suite 304 Minneapolis, MN 55404 (612) 871-2292	Abdhish Bhavsar, MD	3
(246) Retina Consultants of Nevada	653 North Town Center Drive, Suite 518 Las Vegas, NV 89144 (702) 369-0200	Allen B. Thach, MD	8
(248) Retina Consultants PA	1350 South Main Street, Suite 3200 Fort Worth, TX 76104 (817) 332-1782	Gary M. Cowan, MD	4
(154) Retina Consultants PLLC	1220 New Scotland Road, Suite 201 Slingerlands, NY 12159 (518) 533-6550	Paul Beer, MD	3

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(182) Retina Consultants LLC	2450 12th Street Southeast Salem, OR 97302 (503) 371-4350	Andrew Westfall, MD	9
(167) The Retina Center at Pali Momi	98-1079 Moanalua Road, 470 Aiea, HI 96701 (808) 487-8928	Gregg T. Kokame, MD	4
(112) Retina Group of Washington	5454 Wisconsin Avenue, Suite 1540 Chevy Chase, MD 20815 (301) 656-8100	Daniel Berinstein, MD	4
(335) Retina Macula Institute	4201 Torrance Boulevard, Suite 220 Torrance, CA 90503 (310) 944-9393	Ron P. Gallemore, MD	6
(309) Retina Northwest, P.C.	2525 Northwest Lovejoy, Suite 300 Portland, OR 97210 (503) 274-2121	Michael Lee, MD	12
(143) Retina Research Center	3705 Medical Parkway, Suite 420 Austin, TX 78705 (512) 454-5851	Brian B. Berger, MD	5
(128) Retina Specialists	5150 North Davis Highway Pensacola, FL 32503 (850) 476-6759	Sunil Gupta, MD	6
(134) Retina Specialists	6569 North Charles Street, Suite 605 Towson, MD 21204 (410) 296-9700	John Thompson, MD	6
(218) Retina Vitreous Consultants	3501 Forbes Avenue, Suite 500 Pittsburgh, PA 15213 (412) 683-5300	Pamela Rath, MD	13
(149) Retina-Vitreous Center PA	530 Lakehurst Rd, Suite 305 Toms River, NJ 08755 (732) 797-3883	Daniel B. Roth, MD	12
(129) Retina & Vitreous Center of Southern Oregon PC	246 Catalina Drive Ashland, OR 97520 (541) 488-3192	William Rodden, MD	1
(139) Retinal Consultants Medical Group, Inc	3939 J Street, Suite 100 Sacramento, CA 95819 (916) 454-4861	Joel A. Pearlman, MD	22
(127) Retinal Diagnostic Center	3803 S. Bascom Avenue, Suite 104 Campbell, CA 95008 (408) 559-0666	Amr L. Dessouki, MD	2
(204) Rocky Mountain Eye Center	700 West Kent Avenue Missoula, MT 59801 (406) 541-3937	Brian Sippy, MD	14
(507) Royal Victoria Hospital	687 Pine Avenue West, Room M8-07 Montreal, Quebec H3A1A1, Canada (514) 843-1646	Ivan J. Galic, MD	15

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(294) Southern California Desert Retina Consultants	36949 Cook Street, Suite 101 Palm Desert, CA 92211 (760) 340-2394 x229	Clement Chan, MD	6
(229) Southwest Michigan Eye Center	3600 Capital Avenue Southwest, Suite 203 Battle Creek, MI 49015 (269) 979-6383 x1023	Peter J. Colquhoun, MD	6
(277) Soll Eye Associates	10160 Bustleton Avenue, Suite F Philadelphia, PA 19116 (215) 288-5000	David Rho, MD	3
(147) Southeast Retina Center	3685 Wheeler Road, Suite 201 Augusta, GA 30909 (706) 650-0061	Dennis Marcus, MD	16
(245) St. Johns Clinic Eye Specialists	1229 East Seminole, Suite 430 Springfield, MO 65804 (417) 841-0250	X. Kathryn Sun, MD	3
(203) Mayo Clinic Jacksonville	4500 San Pablo Road Jacksonville, FL 32224 (904) 953-2232	Michael W. Stewart, MD	12
(222) TLC Eye Care & Laser Center	1116 W. Ganson Street Jackson, MI 49201 (517) 782-4936	Carmelina Gordon, MD	31
(297) Tennessee Retina, P.C.	345 23rd Avenue North, Suite 350 Nashville, TN 37203 (615) 320-7911	Peter L. Sonkin, MD	5
(295) University of California Irvine Medical Center	118 Med Surge Irvine, CA 92697 (714) 456-7741	Baruch D. Kuppermann, MD	6
(164) UCSD Jacobs Retina Center	9415 Campus Point Drive, Room 141 La Jolla, CA 92037 (858) 534-3513	William R. Freeman, MD	19
(178) Dean McGee Eye Institute	608 Stanton L. Young Boulevard Oklahoma City, OK 73104 (405) 271-6307	Robert Leonard, MD	10
(514) University of Ottawa Eye Institute	501 Smyth Road W6261 Ottawa Ontario K1H 8L6, Canada (613) 737-8574	Brian C. Leonard, MD	7
(317) University of Texas Southwestern Medical Center	5323 Harry Hines Boulevard Dallas, TX 75390 (214) 648-3838	Yu-Guang He, MD	3
(155) The University of Iowa Hospitals & Clinics Department of Ophthalmology	200 Hawkins Drive E318-3, GH Iowa City, IA 52242 (319) 356-3185	Herbert Boldt, MD	5
(172) W. Kellogg Eye Center	1000 Wall Street Ann Arbor, MI 48105 (734) 615-8560	Mark Johnson, MD	5

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(221) USF Eye Institute	12901 Bruce B. Downs Boulevard MDC Box 21 Tampa, FL 33612 (813) 974-3820	Peter R. Pavan, MD	8
(216) University of Rochester Eye Institute	601 Elmwood Avenue, Box 659 Rochester, NY 14642 (585) 273-3937	David A. DiLoreto, Jr., MD	1
(173) University of Utah John Moran Eye Center	65 Mario Capecchi Drive Salt Lake City, UT 84132 (801) 581-4069	Michael Teske, MD	5
(292) University of Virginia	1 Jefferson Park Avenue, Room 2810 B Charlottesville, VA 22908 (434) 243-2852	Brian P. Conway, MD	5
(298) University of Wisconsin	2880 University Avenue, Room L14 Madison, WI 53705 (608) 263-9035	Michael Altaweel, MD	1
(199) Vitreous Retina Macula Consultants of New York	460 Park Avenue 5th Floor New York, NY 10022 (212) 861-9797	James M. Klancnik, MD	1
(506) UBC/VH Eye Care Center	2550 Willow Street, Section B Vancouver, British Columbia V5Z3N9, Canada (604) 875-4253	Andrew B. Merkur, MD	12
(138) Valley Retina Institute	1309 East Ridge Road, Suite 1 McAllen, TX 78503 (956) 631-8875	Victor H Gonzalez, MD	6
(126) Virginia Eye Institute	7301 Forest Ave, Suite 200 Richmond, VA 23226 (804) 285-5305	James Combs, MD	1
(171) Vision Research Center	2300 Holmes Street Kansas City, MO 64108 (816) 404-1800	Nelson Sabates, MD	4
(163) Vitreo-Retinal Consultants & Surgeons PA	530 North Lorraine Street, Suite 200 Wichita, KS 67214 (316) 683-5611	Paul Weishaar, MD	11
(206) Vitreo-Retinal Associates PC	3350 Eagle Park Drive, Suite 105 Grand Rapids, MI 49525 (616) 285-1200	Louis C. Glazer, MD	12
(174) Vitreo Retinal Consultants	6560 Fannin Street, Suite 750 Houston, TX 77030 (713) 524-3434	Matthew Benz, MD	30
(288) Vitreoretinal Associates	1221 Madison Street, Suite 1002 Seattle, WA 98104 (206) 215-3850	David A. Saperstein, MD	4
(310) California Vitreoretinal Research/Stanford University	1225 Crane Street, Suite 202 San Mateo, CA 94025 (650) 323-0231	Darius M. Moshfeghi, MD	5

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(254) Western Carolina Retinal Associate, PA	21 Medical Park Drive Asheville, NC 28803 (828) 255-8978	William Z. Bridges, Jr., MD	17
(213) Weill Cornell Eye Associates	1305 York Avenue New York, NY 10021 (646) 962-2222	Donald D'Amico, MD	1
(184) Wake Forest University Eye Center	Medical Center Boulevard Winston-Salem, NC 27157 (336) 716-4091	Shree Kurup, MD	12
(321) Yale University School of Medicine	40 Temple Street, Suite 3B New Haven, CT 06510 (203) 785-6150	Ron Adelman, MD	2
TOTAL			**1217**

APPEARS THIS WAY
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Study Schedule

WEEK	Screen	Day 1	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
VISIT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
	D −21 to D 0															
Sign Informed Consent	X															
Medical/Ophthalmic History	X															
Physical Exam	X															
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[2]	X[2]					X[2]			X[2]			X[2]				X[2]
ECG/NYHA	X															X
Interval History (AEs & Con Meds)[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect Ophthal/Slit Lamp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP[3]	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
VA (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X[4]	X	X[6]	X	X[6]	X	X[6]	X[6]	X	X[6]	X[6]	X	X[6]	X[6]	X[6]	X
Fundus Photo/ FA	X[5]								X							X
Hematology & Chemistry Panel[7]	X					X			X			X				
Serum Beta-HCG	X															
PT/PTT[7]	X															X
Urinalysis/UPCR[7]	X					X			X			X				X
Serum for antibody[7]	X					X			X			X				X
Study Drug or Sham Injection[8]			X		X	X	X[10]	X	X[10]	X	X[10]	X	X[10]	X	X[10]	X	O[11]
Telephone Safety Check[9]					X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[9,10]

1. AEs were to have been recorded from the time the IC was signed until completion. If a subject withdrew, AEs were recorded until withdrawal or 30 days after the last dose of study drug, whichever was later.
2. NEI VFQ-25 was administered by certified personnel at a contracted call center. Site assisted the subject at the screening visit to initiate the first call to the call center to collect all of the subject's contact information and to complete the first VFQ on the phone prior to randomization and IVT injection; the call center initiated subsequent contact at appropriate visits to complete questionnaire.
3. IOP was measured pre-dose and 30-60 minutes post-injection
4 & 5. Both eyes at screen visit
6. Optional at this visit.
7. Sample was drawn prior to administration of study drug.
8. See Study Drug Administration (protocol Appendix D [Appendix 1.1]) for study drug injection protocol
9. Mandatory telephone safety checks 3 days post injection or sham injection.
10. Subjects assigned to the VEGF Trap-Eye 2Q8 group received sham injections at these visits. A telephone safety check was mandatory after this visit.
11. Optional injection if study eye met specific criteria: increase in central retinal thickness of ≥ 100 µm compared to the lowest previous value as measured by OCT , or a loss from the best previous letter score of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT, or new or persistent fluid as indicated by OCT, or new onset classic neovascularization, or new or persistent leak on FA, or new macular hemorrhage, or 12 weeks had elapsed since the previous injection)

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Table 3 Schedule of Events (Year 2) (continued)

WEEK	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96
VISIT	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	Visit 26	Visit 27
Medical/Ophthalmic History											
Physical Exam											
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[2]					X						X
ECG/NYHA											X
Interval History (AEs & Con Meds)[1]	X	X	X	X	X	X	X	X	X	X	X
Indirect Ophthal/Slit Lamp[5]	X	X	X	X	X	X	X	X	X	X	X
IOP[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
VA (ETDRS)	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X
Fundus Photo/ FA					X						X
Hematology & Chemistry Panel[4]					X						X
Urinalysis/UPCR[4]					X						X
Serum for antibody[4]					X						X
Study Drug Injection[5,6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6]	O[6,8]
Telephone Safety Check[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]

1. AEs should be recorded from the time the IC has been signed until completion. If a subject withdraws, AEs should be recorded until withdrawal or 30 days after the last dose of study drug, whichever is later.
2. NEI VFQ-25 will be administered by certified personnel at a contracted call center who will call the subject on the phone to complete the questionnaire.
3. Measure IOP pre-dose and 30-60 minutes post-injection.
4. Draw sample prior to administration of study drug.
5. See Study Drug Administration (protocol Appendix D [Appendix 1.1]) for study drug injection protocol.
6. Optional injection if study eye meets specific criteria (increase in central retinal thickness of ≥100 µm compared to the lowest previous value as measured by OCT, or a loss from the best previous letter score of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT, or new or persistent fluid as indicated by OCT, or new onset classic neovascularization, or new or persistent leak on FA, or new macular hemorrhage, or 12 weeks have elapsed since the previous injection).
7. Telephone safety check is required for all subjects, regardless of whether an injection was administered.
8. Dosing at visit 27 is optional for all subjects.

Primary efficacy variable: Proportion of subjects who maintained vision at week 52, where a subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score compared to baseline.

Secondary efficacy variables:

- 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 variables:

- Change from baseline in BCVA at week 12
- Change from baseline in CRT (central retina thickness) 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 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 or more 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

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VIEW #2

Study 311523: "A Randomized, Double-Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap-Eye in Subjects With Neovascular AMD"

Short title: VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW #2)

Primary Objective: To assess the efficacy of intravitreally administered VEGF Trap-Eye compared to ranibizumab (in a non-inferiority paradigm) in preventing moderate vision loss in subjects with all subtypes of wet AMD.

This is an ongoing multi-center, double-masked, randomized (1:1:1:1), active-controlled, parallel-group phase 3 study in 186 centers in 26 countries. The study duration is 2 years. The current submission provides the data up to the primary endpoint covering the first 52 weeks (Year 1) of the study.

On Day 1, eligible subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens identical to VIEW #1. Subjects assigned to 2Q8 were to receive the 2 mg injection every 8 weeks with one additional dose at Week 4 and were to receive sham injections at interim monthly visits (ie. every 8 weeks) during Year 1 of the study. Sham injections using a mock procedure including pressure on the eye exerted by a syringe without a needle, were performed without intraocular penetration and thus without injection of any substance. The primary endpoint assessments were conducted at Week 52 before any injections were made during this visit.

As per protocol, the data were analyzed as soon as the Week 52 data for all subjects were available and cleaned, although the study is still ongoing. The Year 2 safety and efficacy assessments will continue under masked conditions. Special precautions were taken and all efforts are made to keep investigators, subjects, and study monitors masked. Only one eye per subject was enrolled in the study. If a subject's fellow (non-study) eye required treatment for AMD at study entry, or during the subject's participation in the study, the fellow eye was allowed to receive any approved treatment (this was not allowed for the study eye). Although the fellow eye may have received treatment, it was not considered an additional study eye. Subjects who received treatment for the fellow eye could remain in the study. Safety of the fellow eye was monitored, and systemic AEs were collected.

The drug formulation and procedure of administration of drug and sham were identical to VIEW #1.

Inclusion and Exclusion criteria-Identical to VIEW #1
The study is conducted in the following countries (number of study centers in brackets): Argentina (6), Australia (7), Austria (3), Belgium (1), Brazil (4), Colombia (4), Czech Republic (5), France (10), Germany (21), Hungary (4), India (15), Israel (10), Italy (14), Japan (15), Latvia (2), Mexico (7), Netherlands (4), Poland (7), Portugal (2), Singapore (4), Slovakia (2), South Korea (6), Spain (16), Sweden (3), Switzerland (4), and United Kingdom (10).

VIEW #2: Table of Investigators

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(40001) Marsden Eye Surgery Centre	Marsden Street 2150 Parramatta Australia Phone: 61 2 96357077	Arnold, Jennifer	10
(40002) The Royal Melbourne Hospital	Ward 4 South, Grattan Street, Parkville Vic 3050 Australia Phone: 61 3 94171079	Daniell, Mark	1
(40003) Save Sight Institute University of Sydney Eye Hospital	8 Maquarie Street, Sydney NSW 2001 Australia Phone: 61 2 9382 7309	Gillies, Mark	2
(40004) Centre for eye research	32 Gisborne Street, East Melbourne, Vic 3002 Australia Phone: 61 3 9929 8393	Guymer, Robyn	8
(40006) Lion eye institute Charles Gardner Hospital	2 Verdun Street, Nedlands WA 6009 Australia Phone: 61 8 93810870	McAllister, Ian	12
(40007) Westmead Hospital Eye Clinic	Level 4a, Block B, Westmead NSW 2145 Australia Phone: 61 2 98457960	Mitchell, Paul	11
(40008) Vision Eye Institute	270 Victoria Avenue Chatswood NSW 2067 Australia Phone: 61 2 9424 9999	Chen, Simon	6
(60001) Prasad Eye Institute	Bhubaneswar, L.V. Patia Bhubaneswar-751 024, Orissa India Phone: +91-674-33987109	Das, Taraprasad	2
(60002) Regional Institute Of Ophhthalmlogy Medical College	88 college street Kolkata-700073 India Phone : 91-33-22190954	Datta, Himadri	14
(60003) Center for Ophthalmic Sciences AIIMS	Ansari Nagar, New Delhi-110029 India Phone: 91-11-26589380	Garg, SP	17
(60004) Post Graduate Institute of Education & Research	PGIMER, Sector 12, Chandigarh Pin 160012 India Phone: 91-172-2755718, 2755717	Gupta, Amod	7
(60005) Prasad Eye Institute L.V.	Prasad Marg Banjara Hills, Hyderabad 500 034 India Phone: 91-40-30612620	Narayanan, Raja	9
(60006) Narayana Netralaya 121/C	Chord Road Rajaji Nagar, 1st R- Block. Bangalore-560010 India Phone: 91-80-23572633	Natesh, Sribhargava	8

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(60007) Aravind Eye Hospital	Anna Nagar Madurai-625020 Tamil Nadu India Phone: 91-452-2530984	Ramaswamy, Kim	13
(60008) Vision Research Foundation	Shankar Netralaya 18, College Road Chennai -600 006 Tamilnadu India Phone: 91-44- 28227607	Sharma, Tarun	10
(60009) Aravind Eye Hospital	Avinashi Road, Coimbatore-641014 TamilNadu India Phone: 91-422-4360400	Narendran, VenKatapathy	16
(60010) Little Flower Hospital Trust	P.B No.-23,Angamali Kerela. India Phone: 91 484 2453223	Thomas, Cherian	11
(60011) Retina Foundation	Near underbridge Shahibag, Ahmedabad 380009, Gujarat India Phone: 91 79 65422199	Nagpal, Manish	7
(60012) Aravind Eye Hospital	Abhisega Pakkam Road, Tavalai Kuppam Junction,CuddaloreRoad,Pondicherry - 605007 India Ph.hone: 91-413- 2619100,	Dhoble, Pankaja	1
(60013) Aditya Jyot Eye Hospital Pvt. Ltd	Plot No.: 153, Road No.:9. Major Parmeshwaran Rd Opp. SIWS College, Gate NO.:3, Wadala,Mumbai, Maharashtra 400 031 India Phone: 91-22-24177600	Natarajan, S	5
(60014) Shroff Eye Hospital Vision Research Centre	222 S.V. Road, Bandra (West) Mumbai 400 050, India. Phone: 91-22-5692 1000	Shroff, Rahul	7
(60015) Dr. Shroff's Charity Eye Hospital	5027, Kedarnath Road, Daryaganj, New Delhi 110002 India Phone: 91-11-43524400	Agarwal, Manisha	3
(20001) Keio University Hospital	35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582 JAPAN Phone: 81-3-3353-1211	Ozawa, Yoko	6
(20002) Gunma University Hospital	3-39-15 Showa-cho, Maebashi, Gunma 371-8511 JAPAN Phone: 81-27-220-7111	Kishi, Shoji	3
(20003 Nagoya City University Hospital	1 Aza kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601 JAPAN Phone: 81-52-851-5511	Ogura, Yuichiro	3
(20004) Shiga University of Medical Science Hospital	Seta tsukinowa-cho, Otsu, Shiga 520-2192 JAPAN Phone: 81-77-548-2111	Ohji, Masahito	4
(20005)	1-1 Kita-11, Nishi-13, Chuo-ku, Sapporo 060-8604	Ogino, Tetsuo	5

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
Sapporo City General Hospital	JAPAN Phone: 81-11-726-2211	Tanaka, Minoru	16
(20006) Juntendo University Urayasu Hospital	2-1-1 Tomioka, Urayasu-shi, Chiba 279-0021 JAPAN Phone: 81-47-353-3111	Terasaki , Hiroko	10
(20007) Nagoya University Hospital	65 Tsurumai-cho, Showa-ku, Nagoya 466-8560 JAPAN Phone: 81-52-741-2111	Yoshimura, Nagahisa	8
(20008) Kyoto University Hospital	54 Kawahara-cho Shogo-in Sakyo-ku, Kyoto 606-8507 JAPAN Phone: 81-75-751-3111	Yuzawa, Mitsuko	10
(20009) Surugadai Nihon University Hospital	1-8-13 Surugadai, Kanda, Chiyoda-ku, Tokyo 101-8309 JAPAN Phone: 81-3-3293-1711	Iida, Tomohiro	10
(20010) Fukushima Medical University Hospital	1 Hikarigaoka, Fukushima 960-1295 JAPAN Phone: 81-24-547-1111	Ishibashi, Tatsuro	5
(20011) Kyushu University Hospital	3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582 JAPAN Phone: 81-92-641-1151	Sakamoto, Taiji	4
(20012) Kagoshima University Medical and Dental Hospital	8-35-1 Sakuragaoka, Kagoshima 890-8520 JAPAN Phone: 81-99-275-5111	PI - Shiraga, Fumio	3
(20013) Kagawa University Hospital	1750-1 Ikenobe Miki-cho, Kagawa 761-0793 JAPAN Phone: 81-87-898-5111	Takahashi, Kanji	4
(20014) Kansai Medical University Hirakata Hospital	2-3-1 Shin-mach, Hirakata, Osaka 573-1191 JAPAN Phone: 81-72-804-0101	Gomi, Fumi	10
(20015) Osaka University Hospital	2-15 Yamadaoka, Suita, Osaka 565-0871 JAPAN Phone: 81-6-6879-5111	Wagle, Ajeet	1
(68001) Khoo Teck Puat Hospital	90 Yishun Central, Singapore (768828) Singapore Phone: 6563793512	San, Ian Yeo, Y	7
(68002) Singapore National Eye Centre (SNEC)	11 Third Hospital Ave Singapore 168751 Singapore Phone: 65 9820-6033	Tan, Nikolle	4
(68003) Tan Tock Seng Hospital (TTSH)	11 Jalan Tan Tock Seng Singapore 308433 Singapore Phone: 65 6379 3512	Park, Kyu-Hyung	4
(56001) Seoul National University Bundang Hospital	166 Gumi-ro, Bundang-gu, Seongnam 463-707 Korea Phone: 82 31 787 7373		

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(56002) Asan Medical Center Department of Ophthalmology	3881-1 Pungnap2-dong, Songpagu Seoul 138-736 Korea Phone: 82 2 3010 3680	Yoon, Young-Hee	9
(56003) Seoul St. Mary's Hospital Department of Ophthalmology	505 Banpo-Dong, Seocho-Gu, Seoul 137-701 Korea Phone: 82 2 590 2758	PLee, Won-K	3
(56004) Seoul National University Hospital, Department of Ophthalmology	101 Daehangno Chongno-gu, Seoul 110-744 Korea Phone: 82 2 2072 2438	Yu, Hyeong-Gon	5
(56005) Gachon University Gil Medical Center Department of Ophthalmology	1198 Guwol-dong, Namdong-gu, Incheon 405-760 Korea Phone: 82 32 460 3750	Nam, Dong-Heun	1
(56006) Korea University Guro Hospital Department of Ophthalmology	Guro 2-Dong, Guro-Gu Seoul 152-703 Korea Phone: 82 2 2626 1276	Huh, Kuhl	1
(44002) Medizinische Universität Innsbruck Universitätsklinik für Augenheilkunde und Optometrie	Anichstraße 35 6020 Innsbruck Austria Phone: 43 51250423720	Kralinger, Martina	2
(44003) Universitätsklinik für Augenheilkunde und Optomerie Wien Medizinische Universität Wien	Währinger Gürtel 18-20 1090 Vienna Austria Phone: 43 1 40 400 7931	Schmidt-Erfurth, UrsulaH	35
(44004) Konventhospital Barmherzige Brueder Linz Augenabteilung,	Seilerstätte 2, 4021 Linz Austria Phone: 43 732 7897 21700	Schönherr, Ulrich	3
(28003) Domaine Universitaire du Sart Tilman Service d' Ophtalmologie	Bat B35 Liege, 4000 Belgium Phone: 32 4 366 72 75	Rakic, Jean-Marie	1
(38002) Oční klinika FN Brno	Jihlavská 20 63 400 Brno Czech Republic Phone: 420 532 233 263	Kolar, Petr	20
(38003) Oční klinika FN Olomouc	I. P. Pavlova 6 775 20 Olomouc Czech Republic Phone: 420 588 443 272	Rehak, Jiri	8
(38005) Oční klinika/Lexum Praha U	Společenské zahrady 3 140 00 Praha 4 Czech Republic Phone: 420 244 016 481	Fiser, Ivan	7
(38006) Oční klinika FNKV	Šrobárova 50 100 34 Praha 10 Czech Republic Phone: 420 267 16 3441	Hamouz, Jan	10

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
(38007) Ocni oddeleni Krajska zdravotni, a.s.- Masarykova nemocnice v Usti nad Labem, o.z.,	Socialni pece 3316/12A, 401 13 Usti nad Labem, Czech Republic Phone: 420 477 112 980	Liehneova, Ivana	1
(16001) Centre d'Ophtalmologie Paradis	Monticelli 433 rue Paradis 13008 Marseille France Phone : 33 (0)4 91 16 22 32	Devin, Francois	15
(16002) Hôpital Lariboisiere service d'ophtalmologie	2 rue Ambroise Paré 75475 Paris Cedex 10 France Phone: 33 (0)1 49 95 24 75	Gaudric, Alain	5
(16003) Cabinet Ophtalmologique	26 Rue Crillon 69006 Lyon France Phone : 33 (0)4 78 89 18 29	Koenig-Supiot, Francoise	1
(16004) CHU de Bordeaux Hôpital Pellegrin Service d'Ophtalmologie	Place Amélie Raba Léon 33076 Bordeaux Cedex France Phone: 33 (0)5 56 79 57 41/58 64	Korobelnik, Jean-François	12
(16005) Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts Centre D'Investigation Clinique	28, rue de Charenton 75571 Paris Cedex 12 France Phone: 33 (0)1 40 02 14 15	Mohand-Said, Saddek	5
(16006) Centre Ophtalmologique Rabelais	12-14 rue Rabelais 69003 Lyon France Phone: +33 (0)4 78 95 09 08	Quaranta El Maftouhi, Maddalena	11
(16007) Centre Ophtalmologique d'Imagerie et de Laser	11 Rue Antoine Bourdelle 75015 Paris France Phone : 33 (0)1 42 84 94 00	Quentel, Gabriel	8
(16009) CHU de Nantes Hôtel-Dieu service d'ophtalmologie	1 Place Alexis Ricordeau 44093 Nantes cedex 1 France Phone: 33 (0)2 40 08 36 56 (34 11)	Weber, Michel	2
(16010) CHU de Dijon Hôpital Général service d'ophtalmologie	3 Rue Faubourg Raines - BP 519 21033 Dijon France Phone: 33 (0)3 80 29 51 73	Creuzot-Garcher, Catherine	3
(10001) Eberhard-Karls-Universität Tübingen Universitäts Augenklinik	Schleichstr.12-16 72076 Tübingen Germany Phone: 49 7071 2983725	Aisenbrey, Sabine	14
(10002) Universitäts-Augenklinik Freiburg	Killianstr. 5 79106 Freiburg Germany Phone: 49 761 2704013	Hansen, Lutz, L	15
(10005) Augenambulanz	Hohenzollernring 72 48145 Münster Germany Phone: 49 251 935-0 +49 251 935-462	Pauleikhoff, Daniel	1
(10006)	Martinistrasse 52	Richard, Gisbert	5

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
Universitätsklinikum Hamburg Eppendorf Klinik und Poliklinik für Augenheilkunde	20246 Hamburg Germany Phone: 49 40 7410-54417		
(10007) Universitätsklinikum Kiel Klinik für Augenheilkunde	Hegewischstrasse 2 24105 Kiel Germany Phone: 49 431 5974834	Roider, Johann	4
(10008) Augenklinik Charite Campus - Benjamin Franklin	Hindenburgdamm 30 12200 Berlin Germany Phone: 0049 30 450 554 001	Foerster, Michael, H	1
(10009) Universitätsklinikum Leipzig AöR Klinik und Poliklinik für Augenheilkunde	Liebigstr. 10-14 04103 Leipzig Germany Phone: 49 341 9721650	Wiedemann, Peter	7
(10010) Universitäts-Augenklinik	Bonn Ernst-Abbe-Str.2 53127 Bonn Germany Phone: 49 228 28715647	Holz, Frank, G	10
(10012) Klinikum rechts der Isar Augenklinik	Ismaninger Str. 22 81675 München Germany Phone: 49(0)894140-2320	Lohmann, Chris, P	11
(10013) Universitäts-Augenklinik Mainz	Langenbeckstr. 1 55131 Mainz Germany Phone: 49 6131 177085	Pfeiffer, Norbert	10
0(10014) Augenklinik Universitätsklinikum Aachen	Pauwelsstr. 30 52074 Aachen Germany Phone: 49 241 808819	Walter, Peter	2
(10015) Universitätsklinikum Essen Zentrum für Augenheilkunde	Hufelandstr. 55 45122 Essen Germany Phone: 49 201 723 3568	Bornfeld, Norbert	2
(10017) Universitätsklinikum Heidelberg Augenklinik	Im Neuenheimer Feld 400 69120 Heidelberg Germany Phone: 49 6221 56 6695	Dithmar, Stefan	7
(10019) Klinik und Poliklinik für Augenheilkunde am Universitätsklinikum Carl Gustav Carus	Fetscherstraße 74 01307 Dresden Germany Phone: 49 351 458 5104	Sandner, Dirk	3
(10021) Universitätsklinikum Regensburg Klinik und Poliklinik für Augenheilkunde	Franz-Josef-Strauss-Allee 11 93053 Regensburg Germany Phone: 49-941-9449201	Gamulescu, Maria-Andreea	2
(10022) Klinikum der Universität zu Köln Zentrum für Augenheilkunde	Kerpener Str 62 50924 Köln-Lindenthal Germany Phone: 49 (0)221 478-4105	Kirchhof, Bernd	12
(10024) Krankenhaus Dresden	Friedrichstr. 41 01067 Dresden Germany	Hachs, Helmut, G	3

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
Friedrichstadt Städtisches Klinikum Augenklinik Akademisches Lehrkrankenhaus der TU Dresden	Phone: 49 351 480 1829		
(10025) Universitatsklinikum Luebeck	Ratzeburger Allee 160 23538 Luebeck Germany Phone: 49 451 500 22 11	Grisanti, Salvatore	1
(10026) Augenklinik Universitatsklinikum Saarland	Kirrberg Str.1 Haus 22 66421 Homburg Germany Phone: 49 6841 16 22387	Seitz, Berthold	2
(10028) Augenklinik, Klinikum Darmstadt	Heidelberger Landstrasse 379 64297 Darmstadt Germany Phone: 49 6841 16 22387	Emmerich, Karl-Heinz	1
(46001) Veszprém Megyei Csolnoky Ferenc Kórház Non-Profit ZRT	Szemészet, Kórház u. 1, H-8200 Veszprém, Magyarország Hungary Phone: 36 70 3791622	Gyory, Jozsef	25
(46002) Bajcsy-Zsilinszky Kórház	Szemészet, Maglódi u. 89-91, 1106 Budapest, Magyarország Hungary Phone: 36 30 242 8550	Kerenyi, Agnes	22
(46003) Budapest Retina Associates Kft	1133 Budapest, Kárpát u. 62-64 Budapest Hungary Phone: 6302211677	Seres, Andras	20
(46004) Semmelweis Egyetem Szemészeti Klinika	Tömő u. 25-29, H-1083 Budapest, Magyarország Hungary Phone: 36 30 2410960	Papp, András	54
(39001) Hadassah Medical Organization Department of Ophthalmology	P.O. Box 12000 Jerusalem, 91120 Israel Phone: 972 26777228	Chowers, Itay	6
(39002) The Tel-Aviv Sourasky Medical Center Department of Ophthalmology	6 Weizman Street Tel-Aviv, 64239 Israel Phone: 972-3-6925773	Goldstein, Michaella	22
(39003) Goldshleger Eye Institute The Chaim Sheba Medical Center at Tel Hashomer	Tel Hashomer, 52621 Israel Phone: 972-52-6667244	Alhalel, Amir	2
(39004) Kaplan Medical Center	Rehovot 76100 Israel Phone: 972 89441353	Pollack, Ayala	11
(39005) Rabin Medical Center	Petach Tikva, 49100 Israel Phone: 972-3-9377199	Siegel, Ruth	14
(39006) Ha'Emek Medical Center - Ophthalmology Department,	Afula Israel Phone: 972 522828432	Sartani, Gil	2
(39007) Assaf Harofeh Medical Center	Zrifin, 70300 Israel	Eting, Eva	12

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
	Phone : 972-57-7345362		
(39008) Meir Medical Center, Ophthalmology Department	Kfar Saba , 95847 Israel Phone : 972 9 7472776	Ferencz, Joseph	6
(39010) Carmel Medical Center Ophthalmology Clinic	Haifa 34362, Israel Phone: 972 4 8250419	Mathalone, Nurit	5
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(22006) Ospedale San Martino Isituto Clinica Oculistica	Viale Benedetto XV, 5 16132 Genova Italy Phone: 0039 01035338322	Ghiglione, Davidina	6
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(22012) Opsedale Luigi Sacco Dipartimento di Scienze Cliniche Università di Milano	via G.B. Grassi, 74 20157 Milano Italy Phone: 0039 02 39042901	Staurenghi, Giovanni	16
(22013) Ospedale Maggiore Policlinico Mangiagalli, Regina Elena-IRCCS U.O. di Oculistica	via M fandi 20122 Millano Italy Phone: 0039 02 50320844	Viola, Francesco	9
(22014) Ospedale di Circolo Fondazione Macchi U.O. di Oculistica	viale Borri, 57 21100 Varese Italy Phone: 0039 0332278217	Azzolini, Claudio	1
(22015) Ospedale Oftalmico Clinica Oculistica Università degli Studi	via Juvarra, 19 10122 Torino Italy Phone: 0039 011 5666185	Grignolo, Frederico	2
(22016) Ospedale San Raffaele IRCCS Unità Operativa di Oculistica	via Olgettina 60 20132 Milano Italy Phone: 0039 26432645	Introini, Ugo	5
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(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
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(76003) Latvijas-Amerikas acu centrs	Tallinas iela 93 Rīga, 1009 Latvia Phone: 371 29282917	Zarinova, Ilze	13
(30001) Leiden University Medical Center Department of Opthalmolgy	Albinusdreef 2 2333 ZA Leiden The Netherlands Phone: 0031 71 526 30 84	Dijkman, G.	6
(30002) University Medical Center St. Radboud Department of Opthalmology	Philips van Leydenlaan 15 6525 EX Nijmegen The Netherlands Phone: 0031 24 361 31 38	Hoyng, Carel, B	13
(30004) Erasmus MC Department of Ophthalmology	PO Box 2040 3000 CA Rotterdam 's Gravendijkwal 230 3015 CE Rotterdam The Netherlands Phone: 0031 10 463 36 91	Vingerling, Hans, R	6
(30006) University Medical Center Groningen Department of Ophthalmology	PO BOX 30.001 9700 RB Groningen Hanzeplein 1 9713 GZ Groningen The Netherlands Phone: 0031 10 463 36 91	Hooymans, J., M	2
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(18004) Klinika Okulistyki Samodzielnego Publicznego Szpitala Klinicznego nr 1 we Wrocławiu	ul. Chałubińskiego 2a 50-368 Wrocław Poland Phone: 48717842427	Misiuk-Hojlo, Marta	10
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(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Randomized Subjects
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(18011) Niepubliczny Zakład Opieki Zdrowotnej „OFTALMIKA"	Ul. Modrzewiowa 15 85-631 Bydgoszcz Poland Phone: 48604226747	Kaluzny, Jozef	6
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(24003) IOBA-Instituto de Oftalmobiología Aplicada Campus Miguel Delibes	Camino del cementerio s/n 47011 Valladolid Spain Phone: 0034 983 184 734	Coco, Rosa María	1
(24004) Hospital General Universitario de Valencia Servicio de Oftalmología	Avda. Tres Cruces, s/n 46014 – VALENCIA Spain Phone: 0034 96 197 20 00	Cervera, Enrique	5
(24005) Hospital Universitario Virgen Macarena Servicio de Oftalmología	Avda. Dr. Fedriani, s/n 41009 SEVILLA Spain Phone: 0034 95 500 91 82	Esteban González, Eduardo	1
(24006) Instituto Tecnológico de Oftalmología Hospital	Nuestra Señora de la Esperanza Avda. de las Burgas, 2 15705, Santiago de Compostela La Coruña Spain Phone: 0034 981 585733	Gomez-Ulla, Francisco	4
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(24012) Instituto Oftalmologico Fernandez Vega Avda	Dres. Fernández-Vega, n 33012 OVIEDO Spain Phone: 0034 985 24 01 41	Alfonso, Jose Fernando	4
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(24014) Hospital Vall d'Hebrón Servicio de Oftalmología	Passeig de la Vall d'Hebrón, 119-129 08035 Barcelona Spain Phone: 0034 93 489 30 00	Garcia-Arumi, Jose	1
(24015) Instituto Universitario Dexeus Instituto Oftalmológcio de Barcelona	Avda. Diagonal 632 08017 Barcelona Spain Phone: 0034 93 241 91 00	Sararols, Laura	14
(24018) Clínica Piñero Glorieta Plus Ultra	1 41013 - Sevilla Spain Phone: 0034 954296543	Pinero, Antonio	1
(24019) Hospital General de Malaga - Carlos Haya (Hospital Civil) Servicio de Oftalmología	Plaza del Hospital Civil s/n 29009 - MALAGA Spain Phone. 0034 951 29 03 36	Hernando, Carlos	4
(24024) FOM Fundacion Oftalmológica del Mediterraneo Bifurcación Pío Baroja	General Avilés, s/n 46015 VALENCIA Spain Phone: 0034 96 232 81 23	Navea, Amparo	3
(24027) Institut de la Macula I de la Retina Centro Medico Teknon Consultoris Vilana	Area desp 117 C/ Vilana 12 08022, Barcelona Spain Phone: 0034 933 933 117	Basauri, Ernesto	3
(34003) Linköping University Hospital Eye Clinic	Entrance 26 Linköping, 58185 Sweden Phone: 004613222340	Frennesson, Christina	2
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(12016) Royal Eye Infirmary Plymouth Hospitals NHS Trust	Apsley Road Plymouth PL4 6PL United Kingdom Phone: 447720718667	Raman, Vasant	3
(12017)	Aston Triangle, Birmingham B4 7ET. United Kingdom	Gibson, Jonathan, M	3

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(43006) Fundación Zambrano	Callao 1046 1o A C1023AAQ Buenos Aires Argentina Phone: (5411) 4813-1919 / 1916	Zambrano, Alberto, D	7
(43010) Organización Médica de Investigación (OMI)	Uruguay 725, PB. C1015ABO Ciudad Autónoma de Buenos Aires Argentina Phone: (5411) 4372-0308	Schlottmann, Patricio, G	25
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(48004) Clinica de Oftalmologia de Cali	cra.47 sur # 8C-94 Cali Colombia Phone: 57-2-5110259	Ocampo, Hugo, H	8
(48006) Fundacion Oftalmologica Nacional	Calle 50 # 13-50 Bogotá Colombia Phone: 57-1-3451754	Rodriguez, Francisco, J	13
(48007) Instituto Nacional de Investigación en Oftalmología	Cra 48 # 19 A 40 Floor 12 Office 1221 Torre Médica Ciudad del Río Colombia Phone: 57-4-3111421 ext. 112	Sanchez, Juan, G	19
(32001) Instituto de Oftalmologia Fundación de Asistencia	Privada Conde de Valenciana I.A.P Chimalpopoca 14 Col. Obrera06800 Mexico City, Mexico Phone: 52(55)54421704	Cano Hidalgo, Rene	1
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Study Schedule

Procedures	Screening Phase	Treatment Phase														Primary Endpoint Year 1
WEEK	Screening	Baseline	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
VISIT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16
DAY	−21 to 0	1														
Informed consent, inclusion/exclusion criteria, demographic data	X															
Medical/ophthalmic history	X															
Physical examination	X															
Vital signs (temperature, blood pressure and pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[1]	X[1]					X[1]			X[1]			X[1]				X[1]
EQ-5D health questionnaire	X															X
ECG/NYHA before dosing	X		X													
Interval history (AEs & concomitant medications)[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy (assess pre- and post-dose)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
IOP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA using ETDRS chart	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus photo/FA	X								X							
DNA blood sampling (optional)		X[13]				X			X			X				X
Hematology & chemistry panel[4]	X															
Serum pregnancy test	X															
Prothrombin time/PTT and INR[4]	X					X			X			X				X
Urinalysis/UPCR[4]	X					X			X			X				X
Serum for antibody[4]	X					X										
Examination by an ENT specialist[14]		X													X[11]	X[12]
Randomization		X[6]														
PK blood sampling prior to injection		X[11]	X	X		X										
Study drug or sham injection[7]		X		X	X	X[4]	X	X[6]	X	X[6]	X	X[6]	X	X[6]	X	O[9]
Telephone safety check[9]		X		X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[5,8]

Procedures	Treatment Phase										End of Study[15]
WEEK	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96/100
VISIT	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	Visit 26	Visit 27
Vital signs (temperature, blood pressure and pulse rate)	X	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[1]					X						X
EQ-5D health questionnaire											X
ECG/NYHA											X
Interval history (AEs & concomitant medications)[2]	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy (assess pre- and post-dose)	X	X	X	X	X	X	X	X	X	X	X
Slit lamp	X	X	X	X	X	X	X	X	X	X	X
IOP[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
BCVA using ETDRS chart	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X
Fundus photo/FA					X						X
Hematology & chemistry panel[4]					X						X
Urinalysis/UPCR[4]					X						X
Serum for antibody[4]											
PK blood sampling prior to injection	X[13]										
Study drug injection[7,9]	O[9]	O[9]	O[9]	O[9]	O[9]	O[9]	O[9]	O[9]	O[9]	O[9]	
Telephone safety check[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	
End of study											X

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AE = Adverse event; ECG/NYHA = Electrocardiogram/New York Heart Association; ETDRS = Early treatment diabetic retinopathy study; NEI VFQ-25 = National eye institute 25-item visual function questionnaire; FA = Fluorescein angiography; IOP = Intraocular pressure; IVT = intravitreal; OCT = Optical coherence tomography; INR = International normalized ratio; PTT = Partial thromboplastin time; UPCR = urine protein creatinine ratio. Visit schedules may deviate by ±3 days. Scheduled visits should not be altered due to the deviation of the previous visit.

1 NEI VFQ-25 to be administered in a quiet room by a person certified to administer the questionnaire.
2 Baseline findings (before the first administration of study drug) and AEs (after the first administration of study drug) should be recorded from the time the informed consent has been signed until completion. If a subject withdraws, AEs should be recorded until withdrawal or 8 weeks after the last dose of study drug, whichever is later.
3 Measure IOP pre-dose and 30-60 minutes post-injection.
4 Draw/collect sample prior to administration of study drug.
5 Mandatory telephone safety checks 3 days post injection or sham injection.
6 Randomization into the study is recommended to occur prior to Visit 2. Randomization number will be assigned by an unmasked physician or an unmasked designee as soon as eligibility criteria are met.
7 See Attachment 14.1 of the study protocol for study drug injection protocol. For further details on drug administration of ranibizumab, which should also serve as a guidance for the administration of VEGF Trap-Eye, refer to the EU Commission/locally approved label for ranibizumab, which is provided in section 2.3 of the Investigator Site File and Section 5.2.2 of the study protocol. Details will also be provided in the study manual.
8 Subjects assigned to the VEGF Trap-Eye 2Q8 group will receive sham injections at these visits. A telephone safety check is mandatory after this visit.
9 Optional injection if study eye meets specific criteria (Increase in central retinal thickness of ≥ 100 µm compared to the lowest previous value as measured by OCT, or a loss of ≥ 5 ETDRS letters from the best previous letter score in conjunction with recurrent fluid as indicated by OCT, or new onset classic neovascularization, or new or persistent leak on FA, or new macular hemorrhage, or 12 weeks have elapsed since the previous injection).
10 If optional injection is performed the telephone safety check must be completed. Telephone safety check is still required if no injection was administered.
11 PK blood samples will be drawn prior to injection and 1 to 4 hours post injection at this visit.
12 If optional injection is not given, PK sampling may be taken at anytime during the visit.
13 Although DNA blood sampling should be done preferably at Baseline visit, it can also be done at a later visit, but no later than at Visit 6.
14 A standardized medical history will be taken concerning chronic airway diseases, prior to study treatment at Visit 2 by an ENT specialist. A careful endoscopy of the nasal airways with a standardized documentation of findings is completing the rhinological investigation of Visit 2. At Visit 6 and at Visit 16, the participants will be reevaluated by an ENT specialist and a nasal endoscopy will be performed.
15 Week 96 in subjects who did not receive an injection within the last 8 weeks prior to Visit 27.
Week 100 in subject who received an injection at Visit 26. An extra interim visit should be performed in these subjects at Week 98.

Primary efficacy variable: Proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in the ETDRS letter score compared to baseline.

Secondary efficacy variables:

- 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 variables:

- Change from Baseline in BCVA at Week 12
- Change from Baseline in central retinal thickness at Week 52
- Proportion of subjects who gained 30 or more letters of vision from Baseline on the ETDRS chart at Week 52
- Proportion of subjects who lost 30 or more letters of vision from Baseline on the ETDRS chart ("severe" vision loss) at Week 52
- Change from Baseline in scores for NEI VFQ-25 subscales (near activities, distance activities, vision dependency) at Week 52
- Change in scores of the EQ-5D questionnaire from screening at Week 52
- Change from Baseline in total lesion area as assessed by FA at Week 52
- Change from Baseline in greatest linear diameter of lesion on FA
- 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 letters of vision at Week 52
- Proportion of subjects who gained 10 or more 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

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication: treatment of patients with wet AMD.

6.1.1 Methods

The main support for efficacy is from the 2 clinical studies, VIEW #1 and VIEW #2.

6.1.2 Demographics

VIEW #1: Demographics (Full Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=301	2Q8 N=301
Age				
Mean (sd)	78.2 (7.6)	77.7 (7.9)	78.4 (8.1)	77.9 (8.4)
Range	56-99	51-94	50-94	49-94
Gender				
Female	172	194	167	178
Male	132	110	134	123
Race				
White	296	295	291	287
African American	1	1	0	1
Asian	0	3	5	4
American Indian	2	0	2	1
Native Hawaiian	1	0	0	1
Not reported	4	5	3	6
Multiple	0	0	0	1
Ethnicity				
Non-Hispanic	297	293	290	289
Hispanic	7	11	11	12
Eye color				
Dark	101	107	106	99
Other	203	195	194	201
Missing	0	2	1	1

VIEW #2: Demographics (Full Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=296	2Q8 N=306
Age				
Mean (sd)	73.0 (9.0)	74.1 (8.5)	74.7 (8.6)	73.8 (8.6)
Range	50-92	50-93	51-93	50-93
Gender				
Female	169	176	147	175
Male	122	133	149	131
Race				
White	213	226	219	217
African American	1	0	1	2
Asian	60	67	61	69
Missing	17	16	15	18
Ethnicity				
Non-Hispanic	239	259	241	251
Hispanic	52	50	55	55
Eye color				
Dark	177	177	176	193
Other	114	132	120	113

VIEW #1: Baseline Disease Characteristics (Full Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=301	2Q8 N=301
Mean Visual Acuity Letter Score	54.0 (13.4)	55.2 (13.2)	55.6 (13.1)	55.7 (12.8)
Mean Retinal Thickness (microns)	266.8	261.8	266.7	269.0
Area of CNV (mm squared)	6.5	6.6	6.5	6.6
Lesion Type				
Occult	115	110	121	118
Min. classic	101	105	97	110
Predom. classic	82	87	81	71
Total Lesion Size	6.99	6.98	6.95	6.98

VIEW #2: Baseline Disease Characteristics (Full Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=296	2Q8 N=306
Mean Visual Acuity Letter Score	53.8 (13.5)	52.8 (13.9)	51.6 (14.2)	52.4 (13.9)
Mean Retinal Thickness (microns)	325.9	334.6	326.5	342.6

Mean area of CNV (mm squared)	7.59	8.25	7.7	7.8
Lesion Type				
Occult	116	123	113	110
Min. classic	104	112	103	106
Predom. classic	70	72	80	88
Missing	1	2	0	2
Mean Total Lesion Size	8.01	8.72	8.17	8.22

6.1.3 Patient Disposition

Safety analysis set (SAF): All subjects who received any study drug.

Full analysis set (FAS): All randomized subjects who received any study drug and had a Baseline and at least one post-Baseline BCVA assessment.

Per protocol set (PP): All subjects in the FAS who received at least 9 injections of study drug or sham and attended at least 9 scheduled visits during the first year, except for those who were excluded because of major protocol violations. A major protocol violation is one that may affect the interpretation of study results (ie. missing two consecutive injections before administration of the 9th injection). Sham injections were counted as doses administered for the purpose of defining the PP. The PP also included subjects without major protocol deviations who discontinued due to treatment failure at anytime during the first 52 weeks of the study. A treatment failure is a subject who had a decrease from Baseline in BCVA of at least 15 letters at two consecutive assessments, 4 weeks apart, during the first 52 weeks of the study.

VIEW #1: Analysis Population

	R0.5Q4	2Q4	0.5Q4	2Q8
Randomized	306	304	304	303
Safety set (SAF)	304	304	304	303
Full analysis set (FAS)	304	304	301	301
Per protocol set (PPS)	269	285	270	265

VIEW #2: Analysis Population

	R0.5Q4	2Q4	0.5Q4	2Q8
Randomized	303	313	311	313
Safety set (SAF)	291	309	297	307
Full analysis set (FAS)	291	309	296	306
Per protocol set (PPS)	269	274	268	270

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ON ORIGINAL

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable was the proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in ETDRS letter score compared to Baseline (ie. prevention of moderate vision loss).

The primary analysis is an evaluation of the non-inferiority of VEGF Trap-Eye to ranibizumab and includes the following conditional sequence of calculations of the confidence intervals for the difference between treatments in proportion of subjects maintaining vision at Week 52:

Comparison 1: VEGF Trap-Eye 2mg q4 weeks versus ranibizumab
Comparison 2: VEGF Trap-Eye 0.5mg q4 weeks versus ranibizumab
Comparison 3: VEGF Trap-Eye 2mg q8 weeks versus ranibizumab

The non-inferiority margin in individual VIEW 1 and VIEW 2 studies was 10%. The primary analysis was a conditional sequence (a priori ordered hypotheses) of statistical evaluation of non-inferiority of VEGF Trap-Eye to 0.5 mg ranibizumab. VEGF Trap-Eye was to be considered non-inferior to ranibizumab if the confidence interval of the difference lay entirely below 10%, where a positive difference favors ranibizumab. These analyses were based on the PP at Week 52. Once the non-inferiority was demonstrated, the superiority of VEGF Trap-Eye to ranibizumab was examined.

VIEW #1: Primary Efficacy Analysis (FAS Population with LOCF)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=301**	**2Q8 N=301**
Subjects With 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)

VIEW #1: Primary Efficacy Analysis (PP Population with observed cases)

	R0.5Q4 N=269	**2Q4 N=285**	**0.5Q4 N=270**	**2Q8 N=265**
Subjects With Maintained vision at Week 52	243/256 (94.9%)	260/274 (94.9%)	241/258 (96.4%)	237/246 (96.3%)
Difference (%) (95.1% CI)		0.0 (-3.7, 3.8)	-1.5 (-5.0, 2.1)	-1.4 (-5.0, 2.2)

VIEW #2: Primary Efficacy Analysis (FAS Population with LOCF)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=296**	**2Q8 N=306**
Subjects With Maintained vision at Week 52	276 (94.9%)	292 (94.5%)	282 (95.3%)	292 (95.4%)
Difference (%) (95.1% CI)		0.4 (-3.3, 4.0)	-0.4 (-4.0, 3.1)	-0.6 (-4.1, 2.9)

VIEW #2: Primary Efficacy Analysis (PP Population with observed cases)

	R0.5Q4 N=269	2Q4 N=274	0.5Q4 N=268	2Q8 N=270
Subjects With Maintained vision at Week 52	246/261 (94.3%)	251/263 (95.4%)	248/257 (96.5%)	253/264 (95.8%)
Difference (%) (95.1% CI)		-1.2 (-4.99, 2.62)	-2.3 (-5.87, 1.38)	-1.6 (-5.31, 2.15)

In Study VIEW #2, the applicant did not adjust the CI to 95.1% for the interim safety look. The Agency did re-adjust the analysis to include a statistical adjustment as shown in the above tables.

Reviewer's Comment:
Both studies met their primary endpoint. When compared to ranibizumab all 3 doses of VEGF Trap-Eye were non-inferior when comparing the proportion of subjects who maintained vision (lost less than 15 letters lost in the ETDRS letter score). However, none of the doses were superior to ranibizumab.

Since the 2mgQ8 dose has fewer injections than the other 2 studied doses, approval is recommended for this dosage which has the theoretical benefit of less injection related risks (ie. endophthalmitis).

6.1.5 Analysis of Secondary Endpoints(s)

If all three VEGF Trap-Eye groups were shown to be non-inferior to ranibizumab on the primary endpoint, additional comparisons of VEGF Trap-Eye groups to ranibizumab were made with respect to secondary endpoints. The secondary efficacy analysis was conducted in the FAS population and was to test for superiority of VEGF Trap-Eye over ranibizumab. A conditional sequence of statistical hypotheses (a-priori ordered hypotheses) was to control for multiplicity for secondary endpoint analyses. The following sequence of analyses was performed:

1. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to subjects' mean change in BCVA as measured by ETDRS letter score from Baseline to Week 52.
2. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to the proportions of subjects who gained 15 or more letters of vision from Baseline to Week 52.
3. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to subjects' mean change in total NEI-VFQ-25 score from Baseline to Week 52.
4. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to subjects' mean change in BCVA as measured by ETDRS letter score from Baseline to Week 52.
5. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to the proportions of subjects who gained 15 or more letters of vision from Baseline to Week 52.
6. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to subjects' mean change in total NEI-VFQ-25 score from Baseline to Week 52.
7. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to subjects' mean change in BCVA as measured by ETDRS letter score from Baseline to Week 52.
8. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to the proportions of subjects who gained 15 or more letters of vision from Baseline to Week 52.

9. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to subjects' mean change in total NEI-VFQ-25 score from Baseline to Week 52.
10. VEGF Trap-Eye 2Q4 was compared to ranibizumab relative to subjects' mean change in CNV area from Baseline to Week 52.
11. VEGF Trap-Eye 0.5Q4 was compared to ranibizumab relative to subjects' mean change in CNV area from Baseline to Week 52.
12. VEGF Trap-Eye 2Q8 was compared to ranibizumab relative to subjects' mean change in CNV area from Baseline to Week 52.

Reviewer's Comment:
For both VIEW #1 and VIEW #2 none of the aflibercept doses were superior to ranibizumab. Thus, the conditional sequence of statistical hypothesis testing for superiority of VEGF Trap- Eye in a confirmatory manner had to stop after the first step. Therefore, all subsequent statistical tests no longer serve any confirmatory statistical hypothesis testing and only give descriptive indications for potential treatment differences.

VIEW #1: Mean Change From Baseline to Week 52 in ETDRS Letter Score in the Study Eye (Full Analysis Set with LOCF)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=301**	**2Q8 N=301**
Baseline				
Mean ETDRS letter score(sd)	54.0 (13.4)	55.2 (13.2)	55.6 (13.1)	55.7 (12.8)
Week 52				
Mean ETDRS letter score (sd)	62.1 (17.7)	66.1 (16.2)	62.4 (16.5)	63.6 (16.9)
Mean change from baseline at Week 52 (sd)	8.1 (15.3)	10.9 (13.8)	6.9 (13.4)	7.9 (15.0)

VIEW #2: Mean Change From Baseline to Week 52 in ETDRS Letter Score in the Study Eye (Full Analysis Set with LOCF)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=296**	**2Q8 N=306**
Baseline				
Mean ETDRS letter score (sd)	53.8 (13.5)	52.8 (13.9)	51.6 (14.2)	51.6 (13.9)
Week 52				
Mean ETDRS letter score (sd)	63.1 (16.6)	60.4 (18.3)	61.3 (17.8)	60.5 (17.5)
Mean change from baseline at Week 52 (sd)	9.4 (13.5)	7.6 (12.6)	9.7 (14.1)	8.9 (14.4)

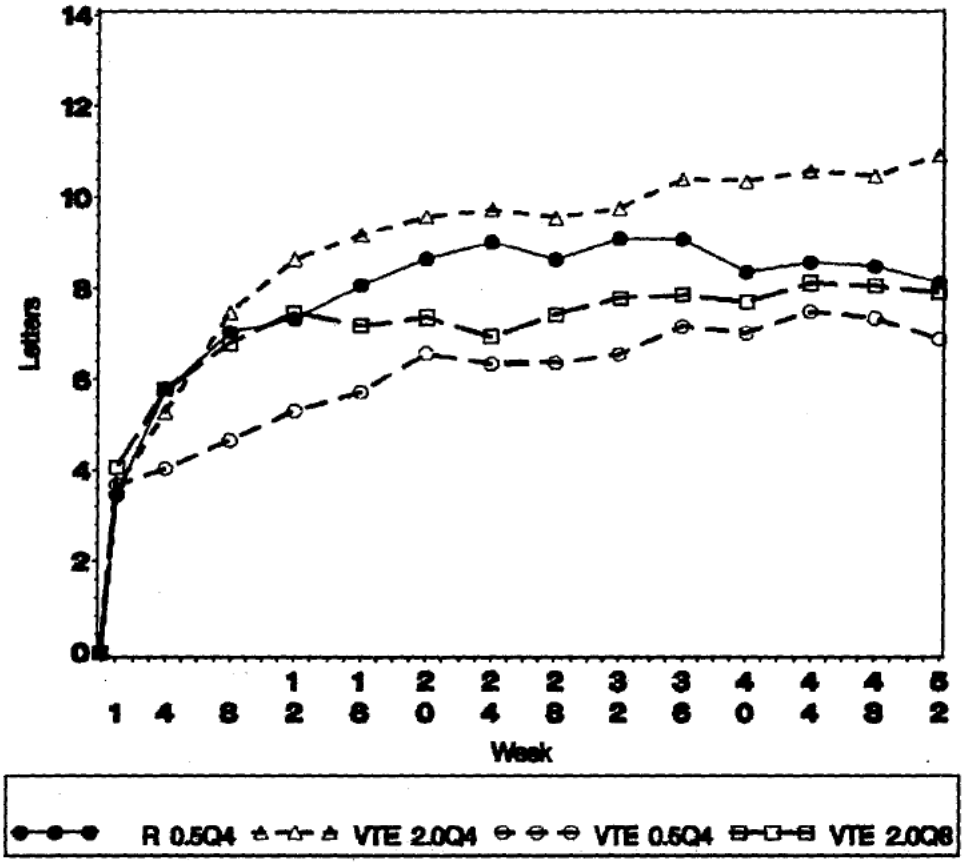
VIEW #1: Mean ETDRS Letter Score (Full analysis Set with LOCF)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=301	2Q8 N=301
Screening	55.2	56.9	56.1	56.8
Baseline	54.0	55.2	55.6	55.7
Week 1	57.4	58.8	59.4	59.8
Week 4	59.7	60.5	59.6	61.5
Week 8	61.0	62.7	60.2	62.5
Week 12	61.3	63.8	60.9	63.2
Week 16	62.0	64.4	61.3	62.9
Week 20	62.6	64.7	62.1	63.1
Week 24	63.0	64.9	61.9	62.6
Week 28	62.6	64.7	61.9	63.1
Week 32	63.1	64.9	62.1	63.5
Week 36	63.0	65.6	62.7	63.5
Week 40	62.3	65.5	62.6	63.4
Week 44	62.5	65.8	63.0	63.8
Week 48	62.5	65.7	62.9	63.7
Week 52	62.1	66.1	62.4	63.6

VIEW #1: Mean Change in ETDRS Letter Score From Baseline (Full analysis Set with LOCF)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=301	2Q8 N=301
Week 1	3.5	3.6	3.7	4.1
Week 4	5.8	5.3	4.0	5.8
Week 8	7.0	7.5	4.7	6.8
Week 12	7.3	8.7	5.3	7.5
Week 16	8.1	9.2	5.7	7.2
Week 20	8.7	9.6	6.6	7.4
Week 24	9.0	9.7	6.3	6.9
Week 28	8.7	9.6	6.4	7.4
Week 32	9.1	9.8	6.6	7.8
Week 36	9.1	10.4	7.2	7.9
Week 40	8.4	10.4	7.0	7.7
Week 44	8.6	10.6	7.5	8.1
Week 48	8.5	10.5	7.4	8.1
Week 52	8.1	10.9	6.9	7.9

VIEW #1: Mean Change From Baseline in Visual Acuity Through Week 52 by Treatment Group (Full Analysis Set with LOCF)



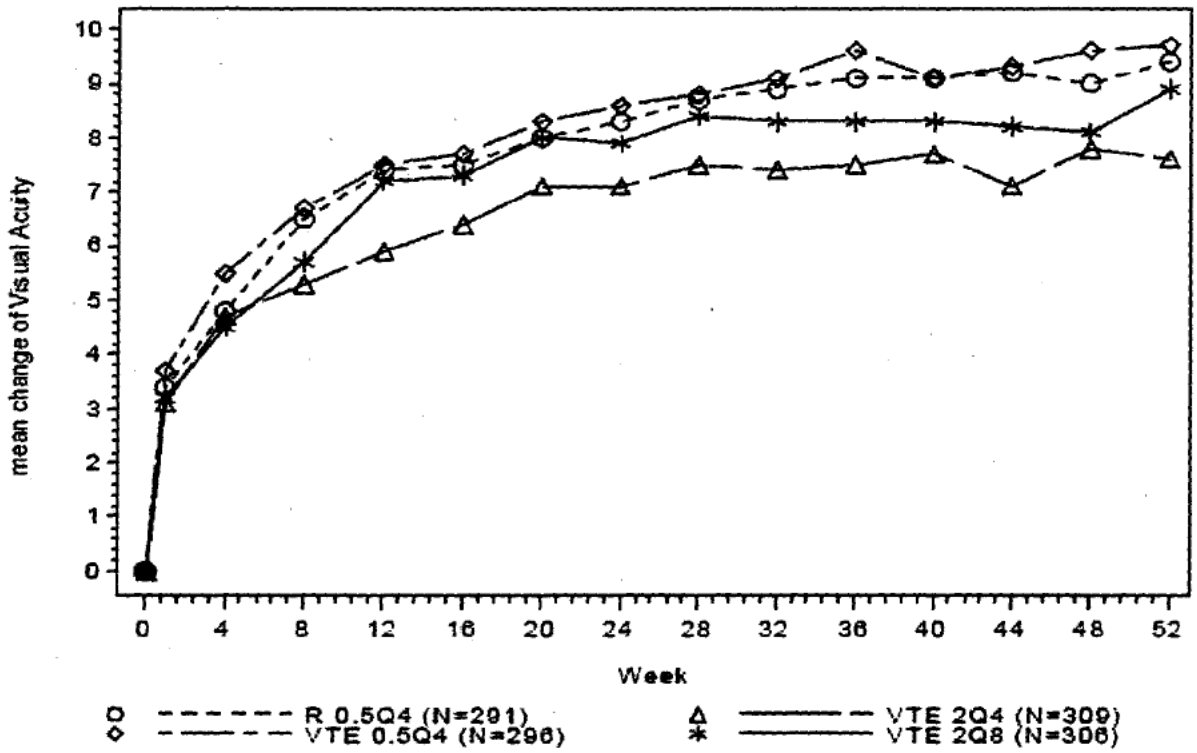
VIEW #2: Mean ETDRS Letter Score (Full analysis Set with LOCF)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=296	2Q8 N=306
Screening	55.0	53.6	52.5	52.1
Baseline	53.8	52.8	51.6	51.6
Week 1	57.2	55.8	55.3	54.8
Week 4	58.6	57.4	57.1	56.1
Week 8	60.2	58.1	58.3	57.3
Week 12	61.2	58.7	59.1	58.7
Week 16	61.3	59.2	59.3	58.9
Week 20	61.8	59.9	59.9	59.6
Week 24	62.1	59.9	60.2	59.5
Week 28	62.5	60.2	60.4	60.0
Week 32	62.6	60.2	60.7	59.9
Week 36	62.9	60.2	61.2	59.9
Week 40	62.8	60.5	60.7	59.9
Week 44	63.0	59.9	60.9	59.8
Week 48	62.7	60.6	61.2	59.7
Week 52	63.1	60.4	61.3	60.5

VIEW #2: Mean Change in ETDRS Letter Score From Baseline (Full analysis Set with LOCF)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=296	2Q8 N=306
Week 1	3.4	3.1	3.7	3.2
Week 4	4.8	4.7	5.5	4.5
Week 8	6.5	5.3	6.7	5.7
Week 12	7.4	5.9	7.5	7.2
Week 16	7.5	6.4	7.7	7.3
Week 20	8.0	7.1	8.3	8.0
Week 24	8.3	7.1	8.6	7.9
Week 28	8.7	7.5	8.8	8.4
Week 32	8.9	7.4	9.1	8.3
Week 36	9.1	7.5	9.6	8.3
Week 40	9.1	7.7	9.1	8.3
Week 44	9.2	7.1	9.3	8.2
Week 48	9.0	7.8	9.6	8.1
Week 52	9.4	7.6	9.7	8.9

VIEW #2: Mean Change From Baseline in Visual Acuity Through Week 52 by Treatment Group (Full Analysis Set with LOCF)



6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

Reviewer's Comment:
There was not a significant interaction between treatment effect and age, gender, race, or baseline visual acuity.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Section 6.1.4

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The current analysis of VIEW #1 and VIEW #2 examined the efficacy of aflibercept at Week 52. The studies are ongoing and efficacy at Year 2 will be available once the studies are completed.

6.1.10 Additional Efficacy Issues/Analyses

Study VGFT-OD-0702 compared 2 different formulations of drug: vial and pre-filled syringe. See section 7.1.1 for full details of study.

VGFT-OD-0702: Mean ETDRS Letter Score (Full Analysis Set with LOCF) Cut Off Date 6/28/2010

	Vial N=45	**PFS N=87**
Baseline	60.2	62.4
Week 8	59.3	62.6
Week 16	60.6	61.7
Week 24	59.9	61.1
Week 32	59.6	60.6
Week 40	60.0	60.6
Week 48	59.1	60.6
Week 56	58.9	60.5
Week 64	58.2	58.8
Week 72	57.1	59.5
Week 80	57.6	59.7
Week 88	56.6	59.6
Week 96	56.8	58.1
Week 104	56.3	58.6
Week 112	56.1	58.6
Week 120	55.2	58.7
Week 128	55.2	58.4
Week 136	55.7	58.3
Week 144	55.6	58.3
Week 152	55.6	58.3
Week 156	55.6	58.3

Mean numbers of injections per subject were similar between the groups (5.8 and 6.2 in the Vial and PFS groups, respectively). The durations that subjects were in the study were similar, with a majority in both groups (74% to 75%) in the study >24 weeks. Mean treatment durations were almost identical between the groups (72.8 to 72.9 weeks). Despite subjects being randomized at different time points, VA over time followed a similar trend in the 2 groups. Most subjects in each group (84% to 87%) maintained vision (<15 letters lost) from baseline of this study to the cut-off date.

Reviewer's Comment:
The two dosage forms of vial and pre-filled syringe are similar in efficacy. (b) (4)

Study VGFT-OD-0702: Change in ETDRS from Baseline of This Study To the Cut-Off Date (All Enrolled Set with LOCF)

Study Visit	Mean Change
Baseline	61.3
Week 8	-0.5
Week 16	-0.3
Week 24	-1.2
Week 32	-1.6
Week 40	-1.6
Week 48	-1.6
Week 56	-1.6
Week 56	-1.7
Week 64	-3.0
Week 72	-2.9
Week 80	-2.6
Week 88	-2.9
Week 96	-3.9
Week 104	-3.7
Week 112	-3.7
Week 120	-4.0
Week 128	-4.1
Week 136	-4.0

Study VGFT-OD-0702: Subjects Who Maintained (<15 Letters Lost) From Baseline of this Study top the Cut-Off Date (All enrolled Set with LOCF)

Study Visit	All Enrolled N=157
Week 8	144 (91.7%)
Week 16	147 (93.6%)
Week 24	150 (95.5%)
Week 32	143 (91.1%)
Week 40	140 (89.2%)
Week 48	143 (91.1%)
Week 56	144 (91.7%)
Week 56	139 (88.5%)
Week 64	139 (88.5%)
Week 72	134 (85.4%)
Week 80	140 (89.2%)
Week 88	132 (84.1%)
Week 96	131 (83.4%)
Week 104	134 (85.4%)
Week 112	131 (83.4%)
Week 120	130 (82.8%)

Week 128	133 (84.7%)
Week 136	132 (84.1%)

Since initially it was thought by DSI that there may be problems with Dr. Marc Micheal's (Site #114) data integrity, the FDA performed the analysis of VIEW #1 excluding his 13 patients.

VIEW #1: Primary Efficacy Analysis (FAS Population with LOCF) Excluding Site #114

	R0.5Q4 N=301	2Q4 N=301	0.5Q4 N=296	2Q8 N=299
Subjects With Maintained vision at Week 52	283 (94.0%)	286 (95.0%)	281 (94.9%)	283 (94.7%)
Difference (%) (95.1% CI)		-1.0 (-4.7, 2.7)	-0.9 (-4.6, 2.8)	-0.6 (-4.3, 3.1)

VIEW #1: Primary Efficacy Analysis (PP Population with observed cases) Excluding Site #114

	R0.5Q4 N=253	2Q4 N=272	0.5Q4 N=246	2Q8 N=245
Subjects With Maintained vision at Week 52	241 (95.3%)	258 (94.9%)	237 (96.3%)	236 (96.3%)
Difference (%) (95.1% CI)		0.4 (-3.3, 4.1)	-1.1 (-4.6, 2.5)	-1.1 (-4.6, 2.5)

Reviewer's Comment:
It was initially thought by DSI that Site #114 did not correctly follow inclusion/exclusion criteria. However upon further examination, DSI was satisfied that there were no data integrity issues. Regardless, removing the 13 patients from Site #114 did not alter the result significantly.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Data Pools for Safety Evaluation for AMD Indication

Study	Phase	Number of Patients	Status
VGFT-OD-0603	1	20	Completed
VGFT-OD-0502	1	51	Completed
VGFT-OD-0702	Phase 1/Phase 2 extension	159	Active but not recruiting

VGFT-OD-0508	2	157	Completed
VIEW #1 (VEGF-OD-0605)	3	1215	Ongoing
VIEW #2 (311523)	3	1204	Ongoing
VGFT-OD-0910	3 extension	178	Ongoing
TOTAL		**2984**	

The above studies were the studies with aflibercept in patients with AMD. Aflibercept has also been studied in patients with DME, CRVO, and oncology indications. This main support for safety and efficacy for the AMD indication comes from the following trials: VIEW #1, VIEW #2, and VGFT-OD-0702 and are therefore the focus of the review.

Study VGFT-OD-0702: "A Randomized, Single-Masked, Long-Term, Safety, and Tolerability Study of Intravitreal VEGF Trap-Eye in Subjects with Neovascular Age-Related Macular Degeneration"

Primary objectives:

- Allow subjects previously enrolled in VGFT-OD-0502, -0508, and -0603 to continue to receive VEGF Trap-Eye after completion of dosing in those studies
- Assess the long-term safety and tolerability of repeated IVT administration of VEGF Trap-Eye in subjects with all sub-types of neovascular AMD for periods of up to 3 years

Secondary objectives:

- Assess the safety of using VEGF Trap-Eye in PFS syringes and Vials
- Assess the frequency of re-treatment
- Assess the effect of continued VEGF Trap-Eye treatment on best corrected visual acuity (BCVA)

VGFT-OD-0702 was a single-masked (to the subject), randomized, multi-center clinical study. Subjects were eligible if they had neovascular AMD and completed dosing in VGFT-OD-0502, VGFT-OD-0508, or VGFT-OD-0603 to enroll in this 3 year study to assess the long-term safety and tolerability of repeated IVT administration of VEGF Trap-Eye in subjects with all sub-types of neovascular AMD. Subjects were initially enrolled to receive VEGF Trap-Eye from a Vial. After 152 subjects had been enrolled, a PFS syringe was introduced as a result of Protocol Amendment 1. From that point, upon enrollment, subjects were randomly assigned in 2:1 ratio to receive:

- 2 mg VEGF Trap-Eye PRN in a 50 µL injection volume from a PFS (Single-use, PFS glass syringes with Snap-off Tip Cap. A plastic plunger rod was attached to the rubber stopper inside the barrel of the syringe. After removing the syringe cap, a 30-gauge needle was attached for administration).
- 2 mg VEGF Trap-Eye PRN in a 50 µL injection volume from a Vial (Sealed, sterile 3 mL Vials of approximately 0.5 mL of VEGF Trap-Eye. The VEGF Trap-Eye was withdrawn into a 1 mL syringe using aseptic technique. A sterile 30-gauge needle was used for intravitreal injection).

Each subject had only 1 eye that was designated as the study eye and was treated in 1 of the 2 treatment arms after enrollment. The other eye was designated as the fellow (non-study) eye and treated if the investigator deemed necessary. Subjects were scheduled to return to the clinical site every 8 weeks. At each visit, the investigator determined the need for IVT injection based on his/her assessment of the subject. If, at any point during the study, in the investigator's opinion, a subject required dosing or evaluation more frequently than every 8 weeks, monthly visits and dosing were permitted. The maximum frequency for injection in the study eye was every 4 weeks. Injection for the fellow eye could be given no less frequently than 6 or 7 days after an injection in the study eye. The fellow eye received the same dose of VEGF Trap-Eye as the study eye. The current result analysis is based on a data cut-off date of 6/28/10. The duration of this study was approximately 39 months. This included 38 months of treatment and 1 month of follow-up. The study is ongoing but not recruiting. Since subjects were randomized upon completion of dosing in their previous study, they were in the current study for varying amounts of time.

Inclusion Criteria:

Subjects' Study Eye:

- Read (if unable to read due to visual impairment, read verbatim by the person administering the informed consent or a family member) understood, and signed the ICF
- Prior participation in 1 of the following studies:
    - VGFT-OD-0502 open-label extension, completing the final/termination visit
    - VGFT-OD-0508, completing visit 16 (week 52)
    - VGFT-OD-0603, completing visit 26 (week 52)
- Willingness to comply with study drug and evaluation procedures
- Willing, committed, and able to return for all clinic visits and complete all study-related procedures

Subjects' Fellow Eye (Not Previously Enrolled):

- CNV secondary to AMD that now required treatment, or prior treatment in the fellow eye with VEGF Trap-Eye in VGFT-OD-0502, VGFT-OD-0508, or VGFT-OD-0603.

Exclusion Criteria:

Subjects' Study Eye:

- Any ocular or systemic adverse events (AEs) during prior study participation that in the investigator's opinion precluded continued intravitreal injection with VEGF Trap-Eye
- Presence of any condition, which, in the investigator's opinion, jeopardized the subject's participation in the study

Subjects' Fellow Eye (Not Previously Enrolled):

- Prior treatment with the following:
    - Besides VEGF Trap-Eye, any prior pegaptanib sodium, bevacizumab, ranibizumab, or other anti-VEGF agent
    - Extrafoveal laser coagulation treatment within 8 weeks of the first dose of VEGF Trap-Eye

  - PDT or IVT administration of triamcinolone acetonide or other steroids within 8 weeks of the first dose of VEGF Trap-Eye
  - Juxtascleral steroids or anecortave acetate within 180 days (6 months) of the first dose of VEGF Trap-Eye
- History of submacular surgery or any surgical AMD interventions
- Any ocular treatment for AMD within 30 days of the first dose of VEGF Trap-Eye
- History of surgery for retinal disease, including (but not limited to), retinal detachment, epiretinal membrane, and pars plana vitrectomy
- Any ocular surgery within 12 weeks of the first dose of VEGF Trap-Eye
- History of vitreous hemorrhage within 4 weeks of the first dose of VEGF Trap-Eye
- Presence of pigment epithelial tears or rips
- Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8.0 diopters or more, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis
- Active ocular infection
- Active ocular inflammation (grade trace or above)
- History or clinical evidence of diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than CNV
- History of corneal transplant or corneal dystrophy
- History of idiopathic or autoimmune associated uveitis
- Uncontrolled glaucoma, in the investigator's judgment
- History of macular hole of stage 3 and above
- Aphakia or pseudophakia with the absence of a posterior capsule (unless it occurred as a result of a yttrium aluminum garnet capsulotomy)

List of Investigators: VGFT-OD-0702

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Enrolled Subjects
(001) Johns Hopkins Hospital School of Medicine Wilmer Eye Institute	600 North Wolfe Street Maumenee 721 Baltimore, Maryland 21287 410-502-9821	Quan D. Nguyen, MD, MSc.	13
(003) Charlotte Eye, Ear, Nose & Throat Asssociates	6035 Fairview Road Charlotte, NC 28210 704-295-3000	David Browning, MD	7
(004) Retina Centers, PC	6585 N Oracle Road Tucson, AZ 85704 520-881-1539	Henry Hudson, MD	5
(005) Tennessee Retina, P.C.	345 23rd Avenue North, Suite 350 Nashville, TN 37203 615-320-7911	Peter Sonkin, MD	5
(006) Dean A. McGee Eye Institute	608 Stanton L. Young Blvd. Oklahoma City, OK 73104 405-271-6307	Robert E. Leonard, MD	9

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Enrolled Subjects
(007) Loma Linda University Health Care	11370 Anderson Street , Suite 1800 Loma Linda, CA 92354 909-558-2168	Joseph Fan, MD	3
(013) Retina Vitreous Associates Medical Group	8641 Wilshire Blvd , Suite 210 Beverly Hills, CA 90211 310-289-2478	David S. Boyer, MD	6
(015) National Ophthalmic Research Institute	6901 International Center Blvd. Ft. Myers, FL 33912 239-938-1284	Joseph Walker, MD	2
(018) Southeast Retina Center	3685 Wheeler Road, Suite 201 Augusta, GA 30909 706-650-0061	Dennis Marcus, MD	10
(019) NorthShore University HealthSystems	2050 Pfingsten Road ,Suite 280 Glenview IL 60026 847-657-1860	Aaron Weinberg, MD	1
(020) Ophthalmic Consultants of Boston	50 Staniford Street ,Suite 600 Boston, MA 02114 Ph: (617)-367-4800	Jeffrey Heier, MD	8
(# 022) Retina-Vitreous Center	530 Lakehurst Rd.,Suite 305 Toms River, NJ 08755 732-797-3984	Daniel Roth, MD	6
(025) Retina Consultants of Houston, P.A.	Texas Medical Center, Scurlock Tower 6560 Fannin #750 Houston, TX 77030 713-524-3434	Matthew Benz, MD	10
(026) Retina Northwest PC	2525 NW Lovejoy, Suite 300 Portland OR 97210 503-274-2121	Michael Lee, MD	2
(027) Center for Retina and Macular Disease	250 Avenue K, SW Winter Haven FL 33880 863-297-5400	Michael Tolentino, MD	10
(028) Black Hills Regional Eye Institute	2800 Third Street Rapid City SD 57701 605-341-2000	Prema Abraham, MD	15
(029) Midwest Eye Institute	200 W. 103rd Street, Suite 1050 Indianapolis, IN 46290 317-805-2179	Thomas Ciulla, MD	7
(030) Associated Retina Consultants	7600 North 15th Street, Suite 155 Phoenix, AZ 85020 602-242-4928 x 115	Clive Sell, MD	2
(032) New England Retina Consultants PC	3640 Main Street, Suite 201 Springfield, MA 01107 413-732-2333	Brad Foster, MD	2
(034) So. California Desert Retina Consultants	36949 Cook Street, Suite 101 Palm Desert, CA 92211 760-327-6225	Clement Chan, MD	2
(035) Medical Center Ophthalmology	9157 Huebner Road San Antonio TX 78240	Michael Singer, MD	4

(Site Number) Name of Study Site	Location/Address	Principal Investigator	Number of Enrolled Subjects
	210-697-2020		
(038) Rocky Mountain Retina Consultants	4400 South, 700 East, Suite 200 Salt Lake City, UT 84107 801-264-4444	David Faber, MD	2
(040) Retinal Consultants of Southern California	1250 La Venta Drive, Suite 208 Westlake Village, California 91361 805-379-0200	Kenneth R. Diddie, MD	1
(043) East Florida Eye Institute	509 SE Riverside Dr., Suite 302 Stuart, FL 34994 772-287-9000	Ronald E. Frenkel, MD	1
(044) Retina Institute of California	301 W. Huntington Drive, Suite 107 Arcadia, CA 91007 626-568-8838	Tom Chang, MD	1
(045) Ophthalmology Associates	1201 Summit Avenue Fort Worth, TX 76102 817-332-2020	John A. Parchue, MD	3
(046) Retina Consultants San Diego	12630 Monte Vista Road, Suite 104 Poway, CA 92064 858-451-1911	Paul Tornambe, MD	4
(047) Retina Research Center	3705 Medical Parkway, Suite 420 Austin, TX 78705 512-454-0138	Brian Berger, MD	3
(048) Ophthalmic Consultants of Long Island (OCLI)	360 Merrick Road, 3rd Floor Lynbrook, NY 11563 516 593-4026	Glenn Stoller, MD	4
(049) Retina Health Center	1567 Hayley Lane Fort Myers, FL 33907 Ph: 239-337-3337	Alexander Eaton, MD	4
(050) Palmetto Retina Center	124 Sunset Court W. Columbia, SC 29169 803-931-0077	John A. Wells, III, MD	1
(051) Valley Retina Institute	1309 East Ridge Road, Suite 1 McAllen, TX 78503 956-631-8875	Victor Gonzalez, MD	2
(052) Cumberland Valley Retina Consultants, PC	1150 Opal Court Hagerstown, MD 21740 301-665-1712	John J. Wroblewski, MD	2
TOTAL			157

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Study Schedule

WEEK	Enrollment[a]	Wk 8	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 56	Wk 64	Wk 72	Wk 80	Wk 88	Wk 96	Wk 104	Wk 112	Wk 120	Wk 128	Wk 136	Wk 144	Wk 152	Wk 156/ET
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Sign Informed Consent[b]	X																				
Randomization[c]	X																				
Medical Ophthalmic History	X																				
Vital Signs (Temperature, BP, Pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interval History (AEs & Con Meds)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect Ophthalmic/Slit Lamp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP[e]	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X
Prot Refraction/VA (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology & Chemistry Panel[f]	X[f]			X[f]			X[f]			X[f]			X[f]			X[f]			X[f]		X[f]
Urinalysis	X[f]			X[f]			X[f]			X[f]			X[f]			X[f]			X[f]		X[f]
Serum for antibody[f]	X[f]			X[f]			X[f]			X[f]			X[f]			X[f]			X[f]		X[f]
VEGF Trap-Eye Injection[g,h,i]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	O[g]	
Telephone Safety Check (3 ±1 day)[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

BP = blood pressure; AE = adverse event; Con Meds = concomitant medications; VA = visual acuity; IOP = intraocular pressure; ETDRS = Early Treatment Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor

a. Enrollment occurred the same day as the completion visit for the original protocol the subject was enrolled but no later than 8 weeks (visit 2) from that date. Exit procedures for the original protocol were used as baseline for this protocol. If enrollment occurred 8 weeks from date of completion of the original study, these assessments and procedures were completed after signed informed consent.
b. Informed consent was signed prior to completion of exit procedures for the original protocol.
c. Randomization occurred at the subject's visit immediately following implementation of amendment 1
d. AEs were recorded from the time informed consent was signed until study completion. If a subject withdrew, AEs were recorded until withdrawal or 30 days after last dose of study drug, whichever was later.
e. Measure IOP pre-injection and 30-60 minutes post-injection.
f. Draw sample prior to administration of study drug
g. Subject was assessed as to whether IVT injection was required at scheduled 8 week and optional monthly visits. O = Optional
h. See Appendix C of the study protocol, in Appendix 1.1 for study drug injection procedures
i. Minimum required assessment for dosing was every 8weeks. Dosing could occur more frequently (every 4 weeks) at the investigator's discretion. Refer to Appendix B (optional visits) of the study protocol in Appendix 1.1 for required procedures.
j. Mandatory telephone safety checks 3 ± 1 days post-injection
k. The fellow eye could be treated at the enrollment visit only if the study eye was not dosed at the same visit.

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Study Schedule for Optional Visits

WEEK	STUDY EYE Weeks 4, 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, and 148	FELLOW EYE Weeks 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 97, 101, 105, 109, 113, 117, 121, 125, 129, 133, 137, 141, 145, 149, and 153 (6 or 7 days post-injection)
Sign Informed Consent		
Medical/Ophthalmic History		
Physical Examination		
Vital Signs (temperature, blood pressure, and pulse)	X	
Interval History (AEs & Con Meds)[c]	X	X
Indirect Ophthalmic/Slit Lamp	X	X
IOP[d]	X[d]	X[d]
Prot Refraction/VA (ETDRS)	X	X
Hematology & Chemistry Panel[e]		
Urinalysis[e]		
Serum for antibody[e]		
VEGF Trap-Eye Injection[f,g,h]	O[f]	O
Telephone Safety Check (3 ±1 day)[i]	X	X

AE = adverse event; Con Meds = concomitant medications; VA = visual acuity; IOP = intraocular pressure; ETDRS = Early Treatment Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor

c. AEs were recorded from the time informed consent was signed until study completion. If a subject withdrew, AEs were recorded until withdrawal or 30 days after last dose of study drug, whichever was later.
d. Measure IOP pre-injection and 30-60 minutes post-injection
e. Draw sample prior to administration of study drug
f. Subject was assessed as to whether IVT injection was required at scheduled 8-week and optional monthly visits. O = Optional
g. See Appendix C of the study protocol in Appendix 1.1 for study drug injection procedures
h. Minimum required assessment for dosing was every 8 weeks. Dosing could occur more frequently (every 4 weeks) at the investigator's discretion. Refer to Appendix B (optional visits) of the study protocol, in Appendix 1.1 for required procedures.
i. Mandatory telephone safety checks 3 ± 1 days post-injection

Analyses for this study were descriptive and exploratory in nature. Their primary focus was to describe the safety and tolerability of VEGF Trap-Eye. Safety variables for this study included AEs, clinical laboratory testing, vital signs, and ophthalmic examinations.

Analysis Sets

All Enrolled Analysis Set

This analysis set included all subjects who were enrolled in the study. It was used to analyze efficacy and safety parameters to characterize the long-term effect of VEGF Trap-Eye.

All Randomized Analysis Set

This analysis set included all subjects who were enrolled in the study and received injection with VEGF Trap-Eye given in a Vial form or VEGF Trap-Eye given in a PFS form after randomization.

Study VGFT-OD-0702: Demographics (All Randomized Set)

	Vial N=50	PFS N=99
Sex		
Male	21	35
Female	29	64
Ethnicity		
Hispanic	1	3
Not Hispanic	49	96
Race		
White	49	99
African American	0	0
American Indian	1	0
Age		
Mean (sd)	79.2 (7.9)	77.0 (8.3)
Min-Max	59-93	55-93

Study VGFT-OD-0702: Disposition

	Vials	PFS	Total
Randomized	50	99	149
Study eye treated	43	87	130

7.1.2 Adequacy of Data

The main support for safety comes from the following 3 trials: VIEW #1, VIEW #2, and VGFT-OD-0702. In these 3 trials there were a total of 2,614 patients.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Three studies were used to support the safety and efficacy of aflibercept injection.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

VIEW #1: Treatment Exposure During the First Year (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Number of Injections During the First Year Including Sham				
1-4	9	1	11	6
5-8	9	6	5	17
9-13	286	297	288	280
Mean (sd)	12.1 (2)	12.5 (1)	12.1 (2)	12.0 (2)
Number of Injections During the First Year Excluding Sham				
Mean (sd)	12.1 (2)	12.5 (1)	12.1 (2)	7.5 (1)
Total Amount of Study Medication During the First Year in mg				
Mean (sd)	6.0 (1)	24.9 (2)	6.0 (1)	14.9 (2)
Min-Max	1-7	6-26	1-7	2-16

VIEW #1: Treatment Duration (Days) in the First Year (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Duration of Study Medication (Days)				
Mean (sd)	350.1 (56)	360.0 (27)	347.8 (63)	347.3 958)
Min-Max	28-378	96-378	28-385	28-379

VIEW #2: Treatment Exposure During the First Year (Safety Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Number of Injections During the First Year Including Sham				
1-4	5	10	9	9
5-8	6	12	8	11
9-13	280	287	280	287
Mean (sd)	12.7 (1)	12.6 (1)	12.7 (1)	12.6 (1)
Number of Injections During the First Year Excluding Sham				

Mean (sd)	12.7 (1)	12.6 (1)	12.6 (1)	7.7 (1)
Total Amount of Study Medication During the First Year in mg				
Mean (sd)	6.2 (1)	24.4 (4)	6.2 (1)	15.1 (3)
Min-Max	0.5-8.0	2.0-28.0	0.5-8.0	2.0-34.0

VIEW #2: Treatment Duration in the First Year (Safety Analysis Set)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=297**	**2Q8 N=307**
Duration of Study Medication (Days)				
Mean (sd)	353.3 (47)	346.5 (61)	349.4 (56)	347.6 (62)
Min-Max	28-378	28-400	28-374	28-385

Study VGFT-OD-0702: Treatment Exposure During the First Year (All Randomized Population)

	Vial N=50	**PFS N=99**
Number of Injections		
Mean (sd)	5.8 (5)	6.2 (5)
Min-Max	0-22	0-23
Total Amount of Study Medication in mg		
Mean (sd)	11.6 (10)	12.4 (10)
Min,Max	0-44	0-46

Study VGFT-OD-0702: Treatment Duration in the First Year (Safety Analysis Set)

	Vial N=50	**PFS N=99**
Duration of Study Medication in Weeks		
Mean (sd)	72.8 (47)	72.9 (47
Min-Max	0-139	0-140

7.2.2 Explorations for Dose Response

See section 6.1.4

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

VIEW #1
Hematology: No trend towards an increase or decrease in mean values over time was seen in the hematology parameters tested in any of the treatment groups. Few subjects had shifts from "normal" at baseline to "abnormal" at subsequent visits. These shifts were within the range of variability expected for this population.

Chemistry: Overall, during the first year of treatment, significant predefined chemistry test abnormalities were observed in a similar frequency for all clinical chemistry parameters in all VEGF Trap- Eye and ranibizumab treatment groups.

VIEW #2
Hematology: Mean and median changes from Baseline over time were analyzed. Generally, none of these analyses showed relevant mean/median changes from Baseline up to Week 52 in the entire study population or within the treatment groups. In addition, no relevant imbalances among treatment groups were observed.

Chemistry: Mean and median changes from Baseline over time (Weeks 12, 24, 36, and 52) were analyzed. Again, none of these analyses showed relevant mean/median changes from Baseline up to Week 52 in the entire study population or within the treatment groups. In addition, no relevant imbalances among treatment groups were observed.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance, and interaction were not performed due to the negligible systemic absorption of aflibercept.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events for this class of drug (anti-VEGF) are known. Refer to Section 2.2 for currently approved products. AEs include: elevated IOP, intraocular inflammation, AEs at the injection site (ie. subconjunctival hemorrhage, scleral pathology, etc.), non-infectious inflammatory eye reactions due to immunogenicity, arterial thromboembolic events, systemic reactions related to immunogenicity, hypertension, problems with nasal mucosa, and RPE tears. Therefore, the following AEs were defined in the protocol as AEs of interest:

Ophthalmic Adverse Events of Interest
The following clinical ophthalmologic observations were to be reported as AEs:

- Any intraocular inflammatory response regardless of suspected etiology

- Any case of new onset IOP of >21 mmHg that does not respond to treatment except the transient pressure rise observed immediately after IVT injection
- Any case of IOP ≥35, at any time, that required treatment
- Any case of corneal edema regardless of suspected etiology
- Any new onset pathology of the sclera, particularly at the injection site
- Any abrupt, clinically significant decrease in BCVA in the study eye

Adverse Events of Interest

- Non-infectious inflammatory eye reactions due to immunogenicity
- Arterial thromboembolic events
- Systemic reactions related to immunogenicity
- Hypertension
- Erosions and ulcerations of the nasal mucosa
- RPE tears
- Embryo-fetotoxicity

7.3 Major Safety Results

7.3.1 Deaths

VIEW #1: Listing of Deaths (Safety Analysis Set)

Subject Number	Treatment Group	Study Day	Number of Days After Last Dose	Cause
145-022	RQ4	19	19	Myocardial infarction
502-001	RQ4	223	83	Hepatic neoplasm
502-008	RQ4	259	35	Lung neoplasm
506-011	RQ4	259	77	CHF
507-019	RQ4	368	33	Aspiration pneumonia
142-027	2Q4	206	15	COPD
314-002	2Q4		54	Respiratory insufficiency
218-008	0.5Q4	99	13	Cerebral hemorrhage
502-003	0.5Q4	80	53	Myocardial infarction
114-018	2Q8	144	4	Hemorrhagic shock
146-016	2Q8	211	15	CVA
182-002	2Q8	313	33	Myocardial infarction
237-003	2Q8	171	31	Arteriosclerosis
284-002	2Q8	113	29	CHF
305-006	2Q8	150	31	Leukemia
309-009	2Q8	233	9	COPD
505-004	2Q8	257	56	CHF

VIEW #2: Listing of Deaths (Safety Analysis Set)

Subject Number	Treatment Group	Study Day	Number of Days After Last Dose	Cause
160020002	RQ4	398	unknown	Esophageal CA
440030022	RQ4	118	3	Acute MI
240090004	0.5Q4	unknown	unknown	unknown
760010013	0.5Q4	46	18	MI
100220010	2Q4	90	35	CVA
600090017	2Q4	359	77	Pyrexia*
600130001	2Q4	251	58	Cardiopulmonary failure
430060004	2Q8	196	27	Lung CA
600040008	2Q8	60	4	Cardiac arrest

- *This patient had experienced a road traffic accident causing polytrauma a few weeks before that fatal pyrexia.*

Study VGFT-OD-0702: Listing of Deaths

Subject Number	Study Day (relative to first dose)	Number of Days After Last Dose	Cause
001-0112	902	43	Unknown at this time
015-1501	748	216	Stroke
018-1801	725	88	Lung CA
020-2007	946	159	Lung CA
027-2709	1006	670	Myocardial infarction
028-2806	603	295	Respiratory failure
044-4401	1175	106	Pulmonary edema
005-0504	1101	564	Lung CA

Reviewer's Comment:
In VIEW #1 there were at total of 17 deaths (5 subjects in the RQ4 group, 2 subjects in the 2Q4 group, 2 subjects in the 0.5Q4 group, and 8 subjects in the 2Q8 group) during Year 1. In VIEW #2 there was a total of 9 deaths (2 subjects in the RQ4 group, 3 subjects in the 2Q4 group, 2 subjects in the 0.5Q4 group, and 2 subjects in the 2Q8 group) during Year 1. In Study VGFT-OD-0702, 8 subjects died during the period from baseline of this study to the cut-off date.

7.3.2 Nonfatal Serious Adverse Events

VIEW #1: Ocular Treatment Emergent SAEs in the Study Eye (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Number of Subjects With At Least 1 Ocular SAE in Study Eye	10 (3.3%)	7 (2.3%)	6 (2.0%)	3 (1.0%)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Endophthalmitis	3	3	0	0
Reduced Visual Acuity	2	1	2	0
Retinal hemorrhage	2	0	0	2
Angle closure glaucoma	0	1	0	0
Cataract	0	0	1	0
Keratitis	0	1	0	0
Macular hole	0	0	1	0
Retinal degeneration	0	1	0	0
Retinal edema	1	0	1	0
RPE tear	0	0	0	1
Retinal tear	1	0	1	0
Incorrect dose administered	1	0	0	0
IOP increased	1	0	0	0

VIEW #1: Non-Ocular Treatment Emergent SAEs (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Number of Subjects With At Least 1 Non-ocular SAE	57 (18.8%)	40 (13.2%)	50 (16.4%)	51 (16.8%)
Infections				
Pneumonia	7	3	2	5
Bronchitis	0	0	1	1
Cellulitis	2	1	1	0
Gastroenteritis	1	0	0	2
UTI	1	2	0	0
Bacterial arthritis	0	0	0	1
Clostridial infection	0	0	0	1
C. diff colitis	0	0	1	0
Endocarditis	0	0	0	1
Escherichia UTI	1	0	1	0
Lobar pneumonia	0	0	0	1
Pyelonepritis	0	1	0	0
Septic shock	0	0	0	1
Sinusitis	0	0	1	0
Fungal sinusitis	0	0	1	0
Staph bacteremia	0	0	0	1
Bacterial UTI	0	0	1	0
Vestibular neuronitis	0	0	1	0
Viral infection	0	0	1	0
Device related infection	1	0	0	0
Diverticulitis	1	0	0	0
Lung infection	1	0	0	0
Pharyngitis	1	0	0	0
Scrotal abscess	1	0	0	0

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Viral pericarditis	1	0	0	0
Cardiac Disorders				
A fib	2	2	0	3
CHF	2	1	2	3
Myocardial infarction	3	1	3	2
CAD	4	0	4	0
Acute myocardial infarction	0	1	1	0
Acute coronary syndrome	0	1	0	0
Aortic valve stenosis	0	0	0	1
Arrhythmia	0	1	0	0
Bradycardia	1	0	1	0
Cardiac arrest	0	0	1	0
Coronary artery occlusion	1	1	0	0
Intracardiac thrombus	0	0	0	1
Mitral valve incompetence	0	0	1	0
Sick sinus syndrome	0	0	0	1
Tachycardia	0	0	0	1
Ventricular tachycardia	0	0	1	0
Unstable angina	1	0	0	0
Chronic cardiac failure	1	0	0	0
Supraventricular tachycardia	1	0	0	0
Neoplasms				
Squamous cell of skin	3	2	1	3
Bladder transitional cell	0	1	1	0
Breast CA	0	0	2	0
Prostate CA	1	0	2	0
Prostate metastatic	0	1	0	1
Breast CA in situ	0	0	1	0
Bronchioalveolar CA	0	1	0	0
CLL	0	1	0	0
Colon CA	0	1	0	0
Leukemia	0	0	0	1
Lung	0	1	0	0
Malignant melanoma	1	0	1	0
Non-small cell lung CA	0	0	1	0
Rectosigmoid CA	0	0	0	1
Renal cell CA	0	0	0	1
Salivary gland CA	0	0	1	0
Thyroid CA	0	0	0	1
Tonsil CA	0	1	0	0
Transitional cell CA	0	0	0	1
Atypical fibroxanothoma	1	0	0	0
Hepatic neoplasm	1	0	0	0
Lung neoplasm malignant	1	0	0	0
Esophageal CA	1	0	0	0
Tumor perforation	1	0	0	0

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Nervous system disorders				
TIA	0	2	5	1
CVA	0	0	1	3
Syncope	1	1	2	0
Carotid artery stenosis	0	2	0	0
Subarachnoid hemorrhage	0	0	1	1
Balance disorder	0	0	0	1
Cerebral artery thrombosis	0	1	0	0
Cerebral hemorrhage	0	0	1	0
Cerebral infarction	0	0	1	0
Ischemic cerebral infarction	0	1	0	0
Metabolic encephalopathy	0	0	1	0
Spinal cord compression	0	0	1	0
Injury and poisoning				
Fall	5	6	4	6
Hip fracture	1	2	2	0
Subdural hematoma	1	0	1	2
Humerous fracture	0	1	1	0
Rib fracture	0	0	1	1
Femur fracture	0	1	0	0
Incisional hernia	0	0	0	1
Pubis fracture	1	1	0	0
Snake bite	0	0	0	1
Subcutaneous hematoma	0	0	0	1
Traumatic brain injury	0	1	0	0
Upper limb fracture	0	0	0	1
Lumbar vertebral fracture	1	0	0	0
Spinal fracture	1	0	0	0
GI disorders				
Gastritis	0	1	0	1
Ischemic colitis	0	0	1	0
Constipation	0	0	1	0
Diarrhea	0	0	1	0
Duodenal ulcer	1	0	1	0
GI motility disorder	0	0	1	0
GERD	0	1	0	0
Hematochezia	0	1	0	0
Hiatus hernia	0	0	0	1
Ileus	0	1	0	0
Lower GI bleed	0	0	0	1
Colonic polyp	1	0	0	0
Erosive gastritis	1	0	0	0
Hemorrhoids	1	0	0	0
Intestinal obstruction	1	0	0	0

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Respiratory disorders				
COPD	2	3	2	2
Pneumonitis	0	1	0	1
Pleural effusion	0	1	0	0
Aspiration pneumonia	1	0	0	1
Pulmonary embolism	0	0	1	0
Pulmonary fibrosis	0	1	0	0
Respiratory failure	0	0	0	1
Apnea attack	1	0	0	0
Metabolism disorder				
Hyponatremia	1	1	1	1
Dehydration	0	0	1	1
DM	0	0	1	0
Inadequate control DM	0	0	0	1
Hyperkalemia	0	0	1	0
Hypokalemia	1	1	0	0
Malnutrition	0	1	0	0
Hypoglycemic shock	0	1	0	0
Vascular disorders				
DVT	0	0	1	1
Aortic aneurysm	1	1	0	0
Aortic stenosis	0	0	0	1
Arteriosclerosis	0	0	0	1
HTN	2	0	1	0
Iliac artery occlusion	0	0	1	0
Peripheral artery occlusion	0	1	0	0
Hemorrhagic shock	0	0	0	1
Aortic aneurysm rupture	1	0	0	0
Orthostatic hypotension	1	0	0	0
General disorders				
Asthenia	0	0	1	0
Catheter site hematoma	0	0	0	1
Chest pain	1	1	0	0
Drug withdrawal syndrome	0	0	1	0
Non-cardiac chest pain	0	1	0	0
Pyrexia	0	0	0	1
Musculoskeletal disorders				
Back pain	0	0	0	1
Intervertebral disc degeneration	0	0	0	1
Intervertebral disc protrusion	0	1	0	0
Lumbar spinal stenosis	1	0	0	1
Osteoarthritis	3	0	0	0

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Spinal column stenosis	1	0	0	0
Spinal osteoarthritis	1	0	0	0
Spondylolisthesis	1	0	0	0
Ear disorders				
Vertigo	0	1	0	1
Merniere's disease	0	0	1	0
Hepatobiliary disorders				
Cholecystitis	0	0	0	1
Chronic cholecystitis	0	1	0	0
Choelithiais	1	1	0	0
Bile duct stone	1	0	0	0
Portal vein thrombosis	1	0	0	0
Renal disorders				
Acute renal failure	0	0	2	1
Calculus ureteric	1	0	0	0
Investigations				
Increased blood glucose	0	1	0	0
Increased blood pressure	0	0	0	1
Psychiatric disorders				
Confusional state	0	0	0	1
Psychotic disorder	0	0	0	1
Mental status changes	2	0	0	0
Blood disorders				
Anemia	0	0	0	1
Congenital disorders				
AV malformation	0	0	0	1
Reproductive disorders				
Cystocele	0	1	0	0

VIEW #2: Ocular Treatment Emergent SAEs in the Study Eye (Safety Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Number of Subjects With At Least 1 Ocular SAE in Study Eye	9 (3.1%)	6 (1.9%)	5 (1.7%)	9 (2.9%)
Visual Acuity Reduced	1	1	1	5
Retinal hemorrhage	1	2	1	1

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Cataract	1	1	0	1
IOP increased	0	0	1	1
RPE tear	1	0	1	1
Cataract nuclear	0	1	0	0
Macular cyst	0	0	0	1
Macular degeneration	0	0	0	1
Macular hole	0	0	1	0
Macular scar	0	1	0	0
Retinal detachment	1	0	1	0
Retinal pigment epitheliopathy	0	0	1	0
Cataract cortical	1	0	0	0
Hyphema	1	0	0	0
PCO	2	0	0	0
Retinal degeneration	1	0	0	0

VIEW #2: Non-Ocular Treatment Emergent SAEs (Safety Analysis Set)

	RQ4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Number of Subjects With At Least 1 Non-ocular SAE	26 (8.9%)	36 (11.7%)	37 (12.5%)	38 (12.2%)
Blood disorders				
Anemia	0	1	1	0
Febrile neutropenia	0	0	0	1
Cardiac disorders				
Acute coronary syndrome	0	2	2	1
Acute myocardial infarction	1	0	0	1
Angina pectoris	1	1	1	0
Arteriosclerosis coronary artery	0	0	0	1
A fib	2	1	0	3
A flutter	0	0	0	1
AV block	0	0	1	0
Cardiac arrest	0	0	0	1
Cardiac failure	0	0	0	1
Cardiovascular insufficiency	0	0	0	1
CAD	0	1	0	0
Myocardial infarction	2	0	3	3
Myocardial ischemia	0	0	0	1
Palpitations	0	1	0	0
Pericarditis	0	1	0	0
Supraventricular tachycardia	0	1	0	0
Ear disorders				

	RQ4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Typmanic membrane disorders	1	0	0	0
Vertigo	0	0	1	0
GI disorders				
Anal fistula	0	0	1	0
Colitis	0	1	0	0
Constipation	0	0	0	1
Diverticulum intestinal	0	0	0	1
Gastric ulcer	0	0	1	0
Gastritis	0	1	0	0
Gastritis erosive	0	0	1	1
Inguinal hernia	0	1	1	1
Intestinal obstruction	0	0	1	0
Large intestine perforation	0	0	0	1
Lower gastrointestinal hemorrhage	0	1	0	0
Pancreatitis acute	0	0	1	1
Small intestinal obstruction	0	0	1	0
General disorders				
Chest pain	1	1	0	0
Death	0	0	1	0
Device dislocation	1	1	0	0
Device malfunction	0	1	0	0
Edema peripheral	1	0	0	1
Pyrexia	0	1	0	0
Hepatobiliary disorders				
Cholecystitis	0	1	0	0
Cholecystitis acute	0	1	0	0
Cholelithiasis	0	0	1	0
Infections				
Appendicitis	1	0	0	0
Bronchitis	1	1	0	1
Dysentery	1	0	0	0
Escherichia sepsis	0	0	0	1
Gastroenteritis	0	0	0	1
Gastroenteritis norovirus	1	0	0	0
Gastroenteritis salmonella	0	0	0	1
Pneumonia	0	2	0	2
Pneumonia pneumococcal	0	1	0	0
Post-operative wound infection	0	0	0	1
Respiratory tract infection	1	0	0	0
Septic shock	0	0	0	1
UTI	1	1	0	0

	RQ4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Injury				
Accident	0	0	1	0
Ankle fracture	0	0	0	1
Burns second degree	0	0	1	0
Clavicle fracture	0	0	0	1
Concussion	0	0	0	1
Contusion	0	0	1	0
Fall	2	0	1	0
Femoral neck fracture	0	0	1	0
Femur fracture	0	0	0	1
Graft thrombosis	0	0	0	1
Head injury	0	1	0	0
Joint injury	1	0	0	0
Lower limb fracture	0	0	1	0
Lumbar vertebral fracture	0	0	0	1
Meniscus lesion	0	0	0	1
Post procedural complication	0	0	1	0
Radius fracture	0	1	0	0
Road traffic accident	0	1	0	1
Skull fractured base	0	1	0	0
Subdural hematoma	0	1	0	0
Upper limb fracture	0	0	2	0
Wound hemorrhage	0	0	0	1
Investigations				
Blood osmolarity decreased	0	1	0	0
EKG QT prolonged	0	1	0	0
Metabolism disorders				
Dehydration	1	0	0	0
Diabetes mellitus	1	0	0	0
Hyperglycemia	1	0	0	0
Musculoskeletal disorders				
Arthralgia	0	1	0	0
Arthritis	0	0	0	1
Dupuytren's contracture	1	0	0	0
Intervertebral disc protrusion	1	0	0	0
Neck pain	0	1	0	0
Rheumatoid arthritis	0	1	0	0
Sjogren's syndrome	0	0	0	1
Synovitis	0	0	0	1
Neoplasms				
AML	0	0	0	1

	RQ4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Basal cell CA	1	0	2	0
Bladder CA	0	0	1	0
Bladder CA recurrent	0	0	1	0
Breast CA	1	0	3	1
Colon CA	0	1	0	0
Colon CA recurrent	0	1	0	0
Lung CA metastatic	0	0	0	1
Lung CA stage 4	0	0	0	1
Lung neoplasm malignant	0	0	1	0
Esophageal CA	1	0	0	0
Ovarian CA	0	1	0	0
Prostate CA	0	0	1	0
Squamous cell CA	0	0	0	1
Nervous system disorders				
Brain edema	0	1	0	0
Cerebral infarction	0	0	1	0
CVA	1	1	0	2
Epilepsy	0	1	0	0
HA	0	1	0	0
Hypertensive encephalopathy	0	0	0	1
Lacunar infarct	0	1	0	0
Nerve root compression	1	0	0	0
Petit mal seizure	0	0	1	0
Syncope	0	1	0	0
TIA	0	2	0	0
7th nerve palsy	0	1	0	0
Renal disorders				
Renal failure	0	1	0	1
Urinary tract obstruction	0	0	0	1
Reproductive disorders				
BPH	0	0	0	1
Uterine hemorrhage	0	1	0	0
Respiratory disorders				
Acute pulmonary edema	1	0	0	0
COPD	0	1	0	1
Cough	0	1	0	0
Dyspnea	0	0	0	1
Pleurisy	0	0	1	0
Pneumothorax	0	1	0	0
Sleep apnea	0	1	0	0
Skin disorders				
Dermal cyst	0	0	1	0

	RQ4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Dermatitis allergic	0	0	0	1
Erythema multifome	0	0	1	0
Rash	0	1	0	0
Skin necrosis	1	0	0	0
Skin ulcer	1	0	0	0

Study VGFT-OD-0702: Ocular SAEs in the Study Eye (All Enrolled Set)

	N=157
VA reduced	4
Retinal hemorrhage	2
Cataract	1
Retinal edema	1
Corneal abrasion	1

Study VGFT-OD-0702: Non-Ocular SAEs (All Enrolled Set)

	N=157
Neoplasms	
Squamous cell of skin	4
Colon CA	2
Head and neck CA	2
Lung CA	2
Prostate CA	2
Bladder CA	1
Breast CA	1
Breast CA recurrent	1
CLL	1
Liver CA	1
Non-small cell lung CA	1
Renal cell CA	1
Small cell lung CA	1
Squamous cell CA	1
Transitional cell CA	1
Cardiac disorders	
A fib	5
Coronary artery stenosis	2
Myocardial infarction	2
Angina pectoris	1
Arteriosclerosis	1
AV block	1
Bradycardia	1
CHF	1
CAD	1
Pericarditis	1

	N=157
Infections	
Pneumonia	3
Bronchitis	2
Cellulitis	1
C. diff colitis	1
Gastroenteritis	1
Sepsis	1
UTI	1
Viral infection	1
Nervous system disorders	
CVA	2
Dementia	2
Basal ganglia hemorrhage	1
Carotid artery stenosis	1
Dizziness	1
HA	1
Lacunar infarction	1
Pre-syncope	1
Syncope	1
TIA	1
GI disorders	
Colonic polyp	1
Diarrhea	1
Duodenal ulcer perforation	1
Enteririst	1
Gastric ulcer	1
Inguinal hernia	1
Intestinal obstruction	1
Injury	
Fall	5
Cervical vertebral fracture	1
Concussion	1
Femoral neck fracture	1
Incisional hernia	1
Periorbital hematoma	1
Pubis fracture	1
Respiratory disorders	
Pulmonary embolism	2
COPD	1
Dyspnea	1
Pleural effusion	1
Pulmonary edema	1
Respiratory failure	1

	N=157
Musculoskeletal disorders	
Osteoarthritis	2
Arthralgia	1
Intervertebal disc protrusion	1
Lumbar spinal stenosis	1
Rotator cuff syndrome	1
Hepatobiliary disorders	
Cholelithiasis	3
Bile duct stone	1
Cholecystitis acute	1
General disorders	
Death	1
Gait disorders	1
Metaplasia	1
Metabolism disorders	
Dehydration	3
Psychiatric disorders	
Hallucination	1
Mental disorder	1
Renal disorders	
Hematuria	1
Renal failure	1
Vascular disorders	
HTN	1
Orthostatic hypotension	1
Blood disorders	
Anemia	1
Endocrine disorders	
Goiter	1
Immune system disorders	
Sarcoidosis	1
Reproductive system disorders	
Prostatic obstruction	1

7.3.3 Dropouts and/or Discontinuations

VIEW #1: Disposition (All Randomized Subjects)

	R0.5Q4	2Q4	0.5Q4	2Q8
Randomized	306	304	304	303
Completed first year of study	284 (92.8%)	293 (96.4%)	277 (91.1%)	276 (91.1%)
Discontinuation from study with first year	22	11	27	27
Adverse event	4	3	5	4
Death	3	1	2	7
Withdrawal by subject	10	5	7	8
Protocol deviation	3	0	3	1
Lost to follow-up	1	2	4	4
Treatment failure	0	0	2	2
Other	1	0	4	1

VIEW #2: Disposition (All Randomized Subjects)

	R0.5Q4	2Q4	0.5Q4	2Q8
Randomized	303	313	311	313
Completed first year of study	276 (91.1%)	281 (89.8%)	274 (88.1%)	284 (90.7%)
Discontinuation from study with first year	27	32	37	29
Adverse event	2	6	8	9
Death	1	3	2	1
Withdrawal by subject	11	15	13	11
Protocol deviation	2	1	1	0
Lost to follow-up	4	1	2	2
Treatment failure	0	0	1	1
Other	7	6	10	5

Study VGFT-OD-0702: Disposition (All Enrolled Set)

	N=149
Subjects Prematurely Terminated From Study	28
Withdrawn Due to AE	4
Investigator Decision	2
Subject Request for Withdrawal	8

Lost to f/u	3
Death	7
Other	4

7.3.4 Significant Adverse Events

See section 7.3.2

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A treatment-emergent adverse event was defined as an event that was observed or reported after administration of study drug that was not present prior to study drug administration or an event that represented an exacerbation of a pre-existing event.

VIEW #1: Ocular Treatment Emergent AE in the Study Eye Occurring In At Least >=5% of Subjects (Safety Analysis Set)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Number of subjects with at least 1 ocular TEAE in study eye	246	228	226	238
Conjunctival hemorrhage	144	109	120	131
Vitreous floaters	33	40	23	21
Eye pain	26	33	27	22
Vitreous detachment	24	26	23	19
Visual acuity reduced	20	24	23	20
Retinal hemorrhage	19	9	17	23
Retinal pigment epitheliopathy	11	16	15	13
Macular degeneration	16	16	17	10
IOP increased	22	14	12	15
Eye irritation	16	13	13	12
Maculopathy	19	10	20	8
EBS	9	8	9	16

VIEW #1: Non-Ocular Treatment Emergent AE in the Study Eye Occurring In At Least >=2% of Subjects (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Number of subjects with at least 1 non-ocular TEAE in study eye	234	220	231	223
Infections	123	96	102	104
Nasopharyngitis	23	33	24	26
Upper respiratory tract infection	13	11	14	18
UTI	17	14	15	13
Bronchitis	16	12	11	17
Sinusitis	8	7	11	11
Influenza	9	7	3	7
Pneumonia	14	5	4	6
Cellulitis	7	3	6	2
Investigations	48	57	59	60
Blood glucose increased	8	9	11	7
Protein urine present	7	7	7	10
Urine protein/creatinine ratio increased	3	6	9	6
Blood urine present	4	7	5	6
Blood pressure increased	4	5	3	9
Nervous system disorders	35	40	47	47
HA	19	11	11	12
Dizziness	5	8	6	7
Injury	42	33	47	45
Fall	15	14	12	16
Contusion	4	1	7	3
GI disorder	52	39	37	40
Nausea	13	12	10	7
Diarrhea	9	11	7	5
GERD	6	2	8	6
Constipation	12	3	5	6
Musculoskeletal disorders	54	30	38	41
Arthralgia	11	10	12	5
Back pain	9	5	6	9
Osteoarthritis	5	1	4	7
Arthritis	9	3	5	2

Respiratory disorders	47	34	25	36
Cough	11	7	2	10
COPD	6	5	5	7
Dyspnea	8	4	5	3
Cardiac disorders	41	30	29	32
A fib	11	5	4	6
Vascular disorders	34	30	26	28
HTN	25	21	21	20
Metabolism disorders	29	24	26	24
Hypercholesterolemia	5	3	5	7
Skin disorders	22	16	25	20
General disorder and administration site condition	19	20	16	22
Neoplasms	22	15	21	22
Basal cell CA	4	4	8	8
Renal disorders	19	11	19	15
Psychiatric disorders	21	10	15	14
Anxiety	7	2	3	4
Immune disorders	8	10	12	16
Seasonal allergy	4	6	9	9
Blood disorders	10	6	14	9
Ear disorders	7	7	6	11
Vertigo	4	5	3	8
Reproductive disorders	3	4	8	7

VIEW #2: Ocular Treatment Emergent AE in the Study Eye Occurring in At Least >=5% of Subjects (Safety Analysis Set)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=297**	**2Q8 N=307**
Number of subjects with at least 1 ocular TEAE in study eye	187	191	182	198
Visual acuity reduced	20	26	34	33
Conjunctival hemorrhage	23	24	37	30
Retinal hemorrhage	29	27	30	27
Macular degeneration	23	27	23	30
Eye pain	27	33	22	21
IOP increased	19	24	15	15
Detachment of RPE	15	18	15	12
Vitreous detachment	9	18	9	15
Cataract	15	16	12	12
Ocular hyperemia	18	12	13	9
Retinal degeneration	11	17	9	7

VIEW #2: Non-Ocular Treatment Emergent AE in the Study Eye Occurring in At Least >=2% of Subjects (Safety Analysis Set)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Number of subjects with at least 1 non-ocular TEAE in study eye	181	231	206	213
Infections	77	72	67	73
Nasopharyngitis	25	14	25	19
Influenza	7	14	8	17
Bronchitis	7	13	9	9
UTI	9	7	6	5
Cystitis	3	6	6	2
Upper respiratory tract infection	6	3	5	5
Investigations	43	63	55	61
Blood glucose increased	1	12	8	8
EKG T wave inversion	5	9	2	7

Cardiac disorders	32	48	35	40
AV first degree block	10	20	14	9
A fib	3	7	1	5
GI disorders	30	40	34	45
Diarrhea	10	8	10	14
Abdominal pain	0	3	1	1
Vomiting	6	4	3	2
Musculoskeletal disorders	31	36	33	39
Back pain	13	14	9	11
Arthralgia	8	7	10	3
Osteoarthritis	4	5	5	6
Nervous system disorders	27	33	26	35
HA	11	9	12	17
Dizziness	9	5	1	3
Vascular disorders	247	33	24	23
HTN	22	22	18	16
Respiratory disorders	24	25	25	24
Cough	7	2	7	3
Injury	19	18	26	27
Fall	9	3	4	2
General disorders	**18**	22	29	13
Pyrexia	8	8	15	5
Metabolism disorders	12	19	16	23
DM	4	7	2	7
Hyperglycemia	2	2	6	2
Skin disorders	18	20	14	14
Renal disorders	5	9	11	13
Psychiatric disorders	7	7	11	10
Blood disorders	11	5	12	10
Anemia	6	4	8	7
Neoplasms	6	8	10	8

Ear disorders	4	7	8	9
Reproductive disorders	4	5	4	8
Surgical procedures	4	7	2	3

Study VGFT-OD-0702: Ocular Treatment Emergent AE Reported by >3 Subjects in the Study Eye (All Randomized Set)

	Vial N=50	**PFS N=99**	**Total N=149**
Number of subjects with events	38	58	96
Retinal hemorrhage	8	8	16
Cataract	7	9	16
VA reduced	8	7	15
Conjunctival hemorrhage	6	8	14
Vitreous floaters	2	7	9
Blepharitis	5	2	7
Macular degeneration	3	4	7
FBS	0	6	6
Vitreous detachment	5	1	6
Eye pain	1	3	4
Eye pruritis	0	4	4
Injection site pain	0	4	4
IOP increased	0	4	4

Study VGFT-OD-0702: Non-Ocular Treatment Emergent AE Reported by >3 Subjects in the Study Eye Occurring (All Randomized Set)

	Vial N=50	**PFS N=99**	**Total N=149**
Number of subjects with events	44	87	131
Blood disorders	1	6	7
Anemia	1	4	5
Cardiac disorders	4	12	16
A fib	2	2	4
Ear disorders	4	3	7
Vertigo	2	3	5

GI disorders	14	28	42
Diarrhea	5	5	10
Nausea	3	4	7
Vomiting	4	1	5
GERD	2	2	4
Dyspepsia	1	3	4
Hepatobiliarty disrders	0	5	5
Cholelithiasis	0	4	4
Immune system disorder	1	9	10
Seasonal allergy	0	7	7
Infections	24	46	70
Nasophayrngitis	5	11	16
Bronchitis	5	9	14
UTI	6	7	13
Sinusitis	2	8	10
Upper respiratory tract infection	4	5	9
Influenza	2	4	6
Pneumonia	2	4	6
Localized infection	0	4	4
Injury	12	23	35
Fall	9	10	19
Contusion	3	2	5
Rib fracture	1	3	4
Investigations	10	32	42
Protein urine present	4	2	6
WBC increased	2	4	6
Blood pressure increased	0	4	4
WBC urine positive	0	4	4
Metabolism disorders	8	14	22
Hypercholesterolemia	2	2	4
DM	2	1	3
Gout	1	2	3
Dehydration	1	1	2
DM inadequate control	0	1	1
Musculoskeletal disorders	13	29	42
Arthritis	2	6	8
Osteoarthritis	4	4	8
Arthralgia	2	5	7
Back pain	2	3	5
Pain in extremity	2	3	5
Osteoporosis	0	4	4
Bursitis	2	2	4

Neoplasm	5	19	24
Basal cell CA	1	5	6
Squamous cell CA of skin	2	2	4
Nervous system disorders	11	21	32
Dementia	2	3	5
Dizziness	1	4	5
Psychiatric disorders	5	11	16
Depression	1	4	5
Insomnia	2	3	5
Respiratory disorders	8	14	22
Cough	3	4	7
Dsypnea	1	3	4
Skin disorders	2	14	16
Rash	0	4	4
Vascular disorders	4	14	18
HTN	1	11	12

7.4.2 Laboratory Findings

Refer to section 7.2.4.

7.4.3 Vital Signs

In VIEW# 1 and #2 the following Vital signs were recorded at each visit: body temperature, pulse, blood pressure, and body weight.

In both studies the mean systolic/diastolic blood pressure, heart rate, and temperature were similar among treatment groups both at Baseline and Week 52 and did not show relevant systematic changes during the course of the study.

7.4.4 Electrocardiograms (ECGs)

VIEW 1:
Electrocardiogram (ECG) variables included heart rate, PR interval, RR interval, QRS duration, QT interval, overall interpretation of ECG (normal/abnormal) and clinical relevant abnormalities were recorded at the beginning of the study (screening/visit 1 [day -21 to day 0]), and at the end of year 1 (week 52/visit 16).

Overall, 42.9%, 43.2%, 43.1%, and 40.9% of subjects in the RQ4, 2Q4, 0.5Q4, and 2Q8 groups, respectively, had normal ECG results at baseline and week 52. At week 52, the overall

frequency of abnormal ECG results varied slightly from baseline and was similar among treatment groups.

VIEW 2:
A 12-lead electrocardiogram evaluation was performed at Screening Visit 1, Visit 3/Week 1, and Visit 16/Week 52. Echocardiogram variables included heart rate, PR interval, RR interval, QRS duration, QT interval, overall interpretation of ECG (normal/abnormal) and clinical relevant abnormalities (no/yes).

Overall, about 40% of the study subjects (between 38.6% in the 0.5Q4 group and 43.5% in the 2Q8 group) entered the study with abnormal ECG findings. At Week 52, the proportion of subjects with any abnormal ECG findings had slightly increased to about 45% in total (between 40.8% in the 0.5Q4 group to 49.6% in the 2Q4 group). Generally, there were no patterns or trends to suggest a difference between the treatment groups.

7.4.5 Special Safety Studies

Nasomucosal examination (ENT sub-study)
A subset of 160 subjects in VIEW #2 was additionally examined by an ENT specialist, including nasal endoscopy (ENT sub-study). The purpose of the ENT sub-study was to better define potential nasomucosal side effects which were reported as histopathologic findings in a toxicology study (VGFT-TX-0511 or COV7369-112). Mucosal symptoms were also observed during ocular or systemic therapy with other anti-VEGF products, (ie. in the Lucentis prescribing information nasopharyngitis is mentioned as a frequently reported non-ocular adverse event). Nasal symptoms are very common in the general population - allergic rhinitis alone has a lifetime prevalence of 20 to 25%. Therefore, a targeted, standardized medical history was taken concerning chronic airway diseases, prior to study treatment at Visit 2 by an ENT specialist. A careful endoscopy of the nasal airways with a standardized documentation of findings was to complete the rhinological investigation of Visit 2. At Visit 6 and Visit 16, the participants were re-evaluated by an ENT specialist. The ENT specialist had to ask for nose bleeds and new nasal symptoms since the last ENT visit, and a nasal endoscopy was performed.

VIEW #2: ENT Sub-Study (Number of Subjects With ENT Treatment Emergent AEs)

	R0.5Q4 N=37	2Q4 N=42	0.5Q4 N=37	2Q8 N=44
Nasal septum deviation	4	2	0	5
Nasal mucosal disorder	1	1	2	4
Rhinorrhea	0	1	2	4
Epistaxis	1	1	1	3
Nasal polyps	1	1	1	2
Nasal turbinate hypertrophy	0	0	1	2
Nasal dryness	0	0	0	1
Nasal mucosal discoloration	0	0	1	1
Nasal edema	0	0	0	1
Paranasal cyst	0	0	1	1

Rhinitis hypertrophy	1	0	0	0
Nasopharyngitis	5	2	4	8
Upper respiratory tract infection	1	1	1	4
Rhinitis	2	0	1	1
Viral rhinitis	0	0	1	1
Acute tonsillitis	1	0	0	0

Reviewer's Comment:
The results of the ENT Sub-study in 160 patients at year 1 did not show an increased rate of nasal erosions or other ENT conditions associated with VEGF Trap-Eye compared to ranibizumab.

Arterial Thromboembolic Events

VIEW#1: Number of Subjects with APTC Arterial Thromboembolic Events Through Year 1 (Safety Analysis Set)

	R0.5Q4 N=304	**2Q4 N=304**	**0.5Q4 N=304**	**2Q8 N=303**
Any APTC event	5 (1.6%)	2 (0.7%)	7 (2.3%)	6 (2.0%)
Non-fatal myocardial infarctions	4	1	4	1
Non-fatal strokes	0	1	2	1
Vascular deaths	1	0	1	4

VIEW#2: Number of Subjects with APTC Arterial Thromboembolic Events Through Year 1 (Safety Analysis Set)

	R0.5Q4 N=291	**2Q4 N=309**	**0.5Q4 N=297**	**2Q8 N=307**
Any APTC event	5 (1.7%)	4 (1.3%)	5 (1.7%)	8 (2.6%)
Non-fatal myocardial infarctions	2	2	2	5
Non-fatal strokes	2	1	1	2
Vascular deaths	1	1	2	1

Reviewer's Comment:
Arterial thromboembolic events were a pre-specified AE of interest because of the association of thromboembolic events and VEGF inhibitors. There was no statistically significant difference between groups. There is no clear trend indentified for a particular dose or interval.

IOP Analysis

VIEW #1: Number of Subjects With An Absolute Value of IOP >= 35mmHg During the Study (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Any Visit	13	13	7	13

VIEW #2: Number of Subjects With An Absolute Value of IOP >=35mmHg During the Study (Safety Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Any Visit	9	9	4	5

VIEW #1: Proportion of Subjects With >=10mmHg Increase in IOP From Baseline to Any Pre-Dose Measurement (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Pre-dose from baseline	12	5	6	7

VIEW #2: Proportion of Subjects With >=10mmHg Increase in IOP From Baseline to Any Pre-Dose Measurement (Safety Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Pre-dose from baseline	7	3	8	7

VIEW #1: Proportion of Subjects With >=10mmHg Increase in IOP (Safety Analysis Set)

		R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Baseline	Post-dose from pre-dose	24	28	14	25
Week 1	Pre-dose from baseline	1	1	0	0
Week 4	Pre-dose from baseline	0	0	0	2
	Post-dose from pre-dose	23	28	24	24
Week 8	Pre-dose from baseline	2	1	1	0
	Post-dose from pre-dose	25	26	20	27
Week 12	Pre-dose from baseline	0	0	1	0
	Post-dose from pre-dose	19	27	25	0
Week 16	Pre-dose from baseline	0	0	1	2
	Post-dose from pre-dose	27	27	25	16
Week 20	Pre-dose from baseline	1	0	0	1
	Post-dose from pre-dose	24	28	17	5
Week 24	Pre-dose from baseline	1	0	2	1
	Post-dose from pre-dose	15	36	17	25
Week 28	Pre-dose from baseline	2	0	1	0
	Post-dose from pre-dose	20	22	18	9
Week 32	Pre-dose from baseline	0	2	3	1
	Post-dose from pre-dose	23	29	15	32
Week 36	Pre-dose from baseline	1	1	0	2
	Post-dose from pre-dose	31	28	22	1
Week 40	Pre-dose from baseline	2	1	1	2
	Post-dose from pre-dose	25	32	18	21
Week 44	Pre-dose from baseline	1	0	0	0
	Post-dose from pre-dose	17	29	18	5
Week 48	Pre-dose from baseline	0	0	1	2
	Post-dose from pre-dose	23	17	19	31
Week 52	Pre-dose from baseline	4	0	1	1
	Post-dose from pre-dose	4	2	4	4

VIEW #2: Proportion of Subjects With >=10mmHG Increase in IOP (Safety Analysis Set)

		R0.5Q4 N291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Baseline	Post-dose from pre-dose	8	10	2	8
Week 1	Pre-dose from baseline	0	0	1	3
Week 4	Pre-dose from baseline	1	0	0	0
	Post-dose from pre-dose	5	11	3	8
Week 8	Pre-dose from baseline	1	0	1	0
	Post-dose from pre-dose	8	8	5	12
Week 12	Pre-dose from baseline	1	0	1	1
	Post-dose from pre-dose	7	8	7	1
Week 16	Pre-dose from baseline	0	0	2	2
	Post-dose from pre-dose	12	6	7	7
Week 20	Pre-dose from baseline	1	0	0	2
	Post-dose from pre-dose	13	8	2	1
Week 24	Pre-dose from baseline	0	0	1	0
	Post-dose from pre-dose	8	5	5	6
Week 28	Post-dose from pre- dose	8	10	4	1
Week 32	Post-dose from pre-dose	6	7	6	5
Week 36	Pre-dose from baseline	2	0	0	3
	Post-dose from pre-dose	10	9	4	2
Week 40	Pre-dose from baseline	2	1	1	1
	Post-dose from pre-dose	7	7	3	7
Week 44	Pre-dose from baseline	1	0	0	0
	Post-dose from pre-dose	8	6	6	1
Week 48	Pre-dose from baseline	2	1	3	1
	Post-dose from pre-dose	8	7	5	3
Week 52	Pre-dose from baseline	0	0	1	1
	Post-dose from pre-dose	3	0	1	2

Reviewer's Comment:
There was no clear trend observed between groups. The majority of IOP increases appeared to be post-dose measurements and secondary to the injection procedure itself.

7.4.6 Immunogenicity

For both VIEW #1 and VIEW #2 samples for ADA (anti-drug-antibody) were taken at Screening and subsequently on Weeks 12, 24, 36, and 52. All samples were drawn prior to injection of study drug.

VIEW#1: Number of Subjects With Anti-VEGF Trap Antibodies By Treatment Group (Safety Analysis Set)

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Negative	287	291	290	297
Positive	15 (4.9%)	13 (4.3%)	11 (3.6%)	6 (2.0%)
Not drug induced	5	3	8	5
Transient	7	7	3	1
Persistent	3	3	0	0
Missing*	2	0	3	0

*Subjects with no sample collection of subjects with missing post-baseline sample.

VIEW#2: Number of Subjects With Anti-VEGF Trap Antibodies By Treatment Group (Safety Analysis Set)

	R0.5Q4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Negative	280	285	277	303
Positive	8 (2.7%)	15 (4.9%)	16 (5.4%)	3 (1.0%)
Not drug induced	3	8	8	1
Transient	3	2	4	1
Persistent	2	5	4	1
Not applicable	3	9	4	1

Reviewer's Comment:
These results show that the observed levels of immunogenicity were relatively low and similar between the different groups, including the RQ4 group in which subjects were not administered VEGF Trap-Eye. Furthermore, some subjects were positive even before exposed to the drug at baseline.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not performed.

7.5.2 Time Dependency for Adverse Events

Not performed.

7.5.3 Drug-Demographic Interactions

See section 6.1.7.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not studied.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not studied.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Because of the low absorption of aflibercept, no carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

This drug has not been tested in pregnant women.

7.6.3 Pediatrics and Effect on Growth

This drug was not tested on a pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Aflibercept is a non-narcotic and does not have abuse potential.

7.7 Additional Submissions

A 4 month safety update was submitted on 6/16/11.

The update presented the updated safety data from all studies in VEGF Trap-Eye intravitreal (IVT) formulation that were ongoing at the time of the original BLA, which comprise 7 studies across 3 clinical programs:

- Neovascular AMD (N=2576): the 2 pivotal phase 3 studies (VGFT-OD-0605 [VIEW 1] and 311523 [VIEW 2]), and 2 extension studies (the phase 1/2 extension study, VGFT-OD-0702, and the phase 3 extension study, VGFT-OD-0910).
- Diabetic Macular Edema (DME) (N=219): phase 2 DME study (VGFT-OD-0706)
- Central Retinal Vein Occlusion (CRVO) (N=366): 2 phase 3 CRVO studies (VGFT-OD-0819 [COPERNICUS] and 14130 [GALILEO]).

The data from the 7 studies across 3 therapeutic indications encompasses an exposure of VEGF-Trap eye to approximately 3,000 subjects. The overall assessment of these data shows that VEGF Trap-Eye continues to be well tolerated, with a favorable safety profile consistent with the safety data previously described in the ISS. In general, ocular serious adverse events (SAEs) were similar in type and incidence to those reported in the ISS and were typical of those reported in the underlying disease conditions. In the case of VIEW 1 and VIEW 2 they were consistent with the older study populations, with the ophthalmic condition being treated, or with the study procedure. In the case of VGFT-OD-0702 and VGFT-OD-0910 there were no new ocular SAEs in the study eyes. In the DME and CRVO studies, they were reported at a low frequency, and at comparable or higher frequency in the control groups (laser group for the VGFT-OD-0706 study and sham Q4 group for the VGFT-OD-0819 study). There are 8 SAEs of Endophthalmitis described in the current update; 3 of which were reported previously in the ISS.

Since the last safety update, no trend relative to dose or treatment was observed in the number of deaths occurring during the active study periods among the ongoing studies. No new deaths were reported for VGFT-OD-0819 and study 14130 (GALILEO). In the other studies, new deaths occurred at a low frequency, and most were unrelated to the study drug or procedure as determined by the investigator.

8 Post-marketing Experience

Because aflibercept is not marketed in any country, no sources of AE information exist, except for clinical study reports of the trials that were conducted for its development.

9 Appendices

9.1 Literature Review/References

A pub med search did not reveal any new information on aflibercept.

9.2 Advisory Committee Meeting

Since this is a NME (new molecular entity) there was an advisory committee on June 17, 2011. The following questions were presented to the committee:

1) Do you think adequate safety and efficacy for aflibercept injection has been demonstrated for the treatment of neovascular AMD?

The committee unanimously (all 10 voting members) agreed that adequate safety and efficacy for aflibercept injection has been demonstrated for the treatment of neovascular age-related macular degeneration.

2) If yes, on which study(ies) are you basing your decision?

The majority of the committee based their decision on both View# 1 and View#2 studies.

3) If not, what additional study(ies) should be performed? Do you have any suggestions regarding trial design?

Not applicable.

4) What dosing should be approved (0.5mg Q4, 2mg Q4, or 2mg Q8)? If recommend approving a Q8 schedule should patients be monitored Q4?

The committee recommended 2mg every eight weeks (Q8) with an extra dose at month 2 (2mg monthly for 3 months then once every 2 months). The majority of the committee agreed that monitoring should be at the discretion of the physician and not be required.

5) Elevations in IOP following repeated dosing of VEGF-inhibitors has been reported in the literature and is seen in low frequency in the trials of aflibercept, do you have recommendations of ways to handle the issue?

No recommendations.

6) Do you have any suggestions concerning the proposed draft labeling of the product?

In summary, the committee suggested the following:

- In the dosage and administration section, state the loading dose of 3 initial monthly injections of 2mg first, then 2mg once every 2 months.
- The refrigerated temperature range should be defined.
- Information on how to switch patients from previous VEGF inhibitor medications to aflibercept.

9.3 Comments to be sent to Applicant:

The applicant should provide clinical information from a 1-year (minimum) clinical study to support that there are no adverse effects on the corneal endothelium following the intravitreal administration of aflibercept.

9.4 Labeling Recommendations

(b) (4)

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Signatures:

Reviewer Signature _____ 7/29/11.
Sonal D. Wadhwa, MD

Supervisor Signature _____ 7/29/11 Concurrence Yes ✓ No ___
William Boyd, MD

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Study #1: VIEW 1 Indication: Wet AMD Study #2: VIEW 2 Indication: Wet AMD	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	The VIEW #2 study protocol was almost identical to the US study (VIEW #1). The demographics of VIEW #2 were obviously different from VIEW #1 however the results should be applicable.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		Have not submitted data for endothelial cell counts
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric waiver (b) (4) (b) (4) because it is an adult related condition
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				Defer to Stats
34.	Are all datasets to support the critical safety analyses available and complete?				Defer to Stats
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				Defer to Stats
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all			X	Foreign studies are

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				included; thus, no IRB

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The applicant will need provide clinical information from a 1-year (minimum) clinical study to support that there are no adverse effects on the corneal endothelium following the intravitreal administration of aflibercept. It would be acceptable to provide this information post-approval.

Sonal D. Wadhwa, MD — 3/23/11.
Reviewing Medical Officer — Date

William Boyd, MD — 3/23/11
Clinical Team Leader — Date