# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125387Orig1s000

# MEDICAL REVIEW(S)

Celltrion Exhibit - 1050 Pg. 001
Celltrion, Inc. v. Regeneron Pharmaceuticals, Inc.

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) (b) (4) On September 15, 2009, a Type C meeting (telecon) was held to discuss the status of/ development plans for Regeneron's (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. (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. 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 (b) (4) when stored at 2-8°C.

The application originally proposed (b) (4) (vials (b) (4) (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 (b) (4) facility was conducted from (b) (4). (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)

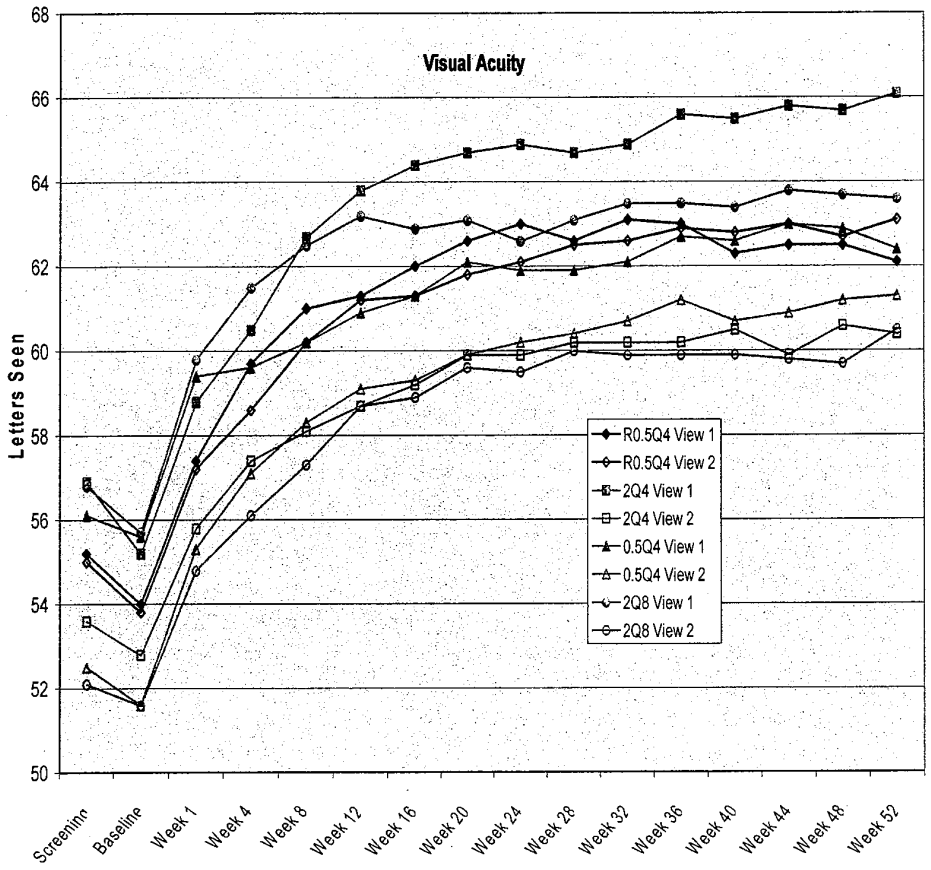
| | **R0.5Q4** | **2Q4** | **0.5Q4** | **2Q8** |
|---|---|---|---|---|
| | **N=269** | **N=285** | **N=270** | **N=265** |
| Subjects With Maintained vision at Week 52 | 243/256 | 260/274 | 241/258 | 237/246 |
| | (94.9%) | (94.9%) | (96.4%) | (96.3%) |
| Difference (%) (95.1% CI) | | 0.0 | -1.5 | -1.4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

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

## 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<br>a. Turbidity<br>b. Visible assessment of particulates | Visual inspection<br>Ph. Eur. 2.2.1, Ph. Eur. 2.9.20 | a. Not greater than reference standard III<br>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<br>a. % main band<br>b. % non-reduced band 1 (NR1) | Slab-gel electrophoresis | a. Aflibercept main band (b) (4) total band area<br>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<br>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<br>a. % main band<br>b. % non-reduced band 1 (NR1) | Slab-gel electrophoresis | a. Aflibercept main band (b) (4) total band area<br>(b) (4) |
| Purity by Size Exclusion HPLC<br>a. % main peak<br>b. % aggregate | Size exclusion HPLC/UV | a. Aflibercept main peak (b) (4) total peak area<br>b. (b) (4) aggregate |
| Isoelectric Focusing<br>a. Profile<br>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.<br>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<br>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:




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 (b) (4) VEGF Trap drug substance (b) (4) (b) (4)

**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. (b) (4)

**CONTROLS OF CRITICAL STEPS AND INTERMEDIATES**
Aflibercept DS for ophthalmic use via intravitreal administration is produced (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<br>USP<61><br>Ph. Eur. 2.6.12 | ≤ 10 CFU/10 mL |
| Endotoxin Content | USP <85>, Ph. Eur. 2.6.14<br>Limulus Amebocyte Lysate<br>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 (b) (4)

## II. DRUG PRODUCT

From BLA Section 5.2:

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

**CONTAINER CLOSURE INTEGRITY TESTING -** (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) |

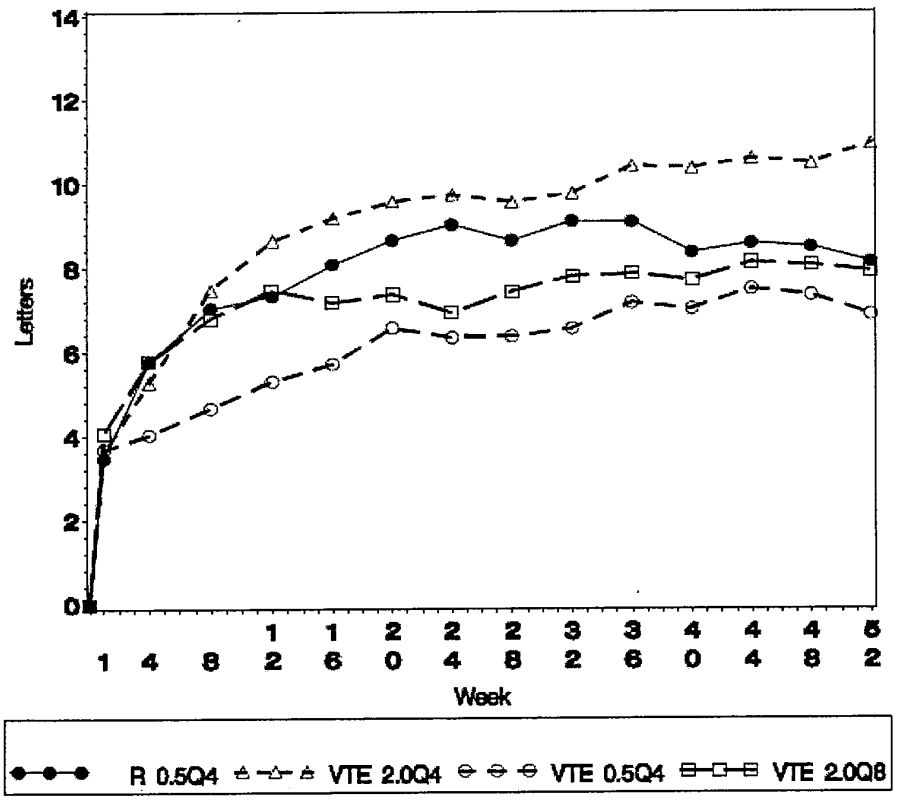
## VIEW #1: Mean ETDRS Letter Score (Full analysis Set with LOCF)

| | **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) |

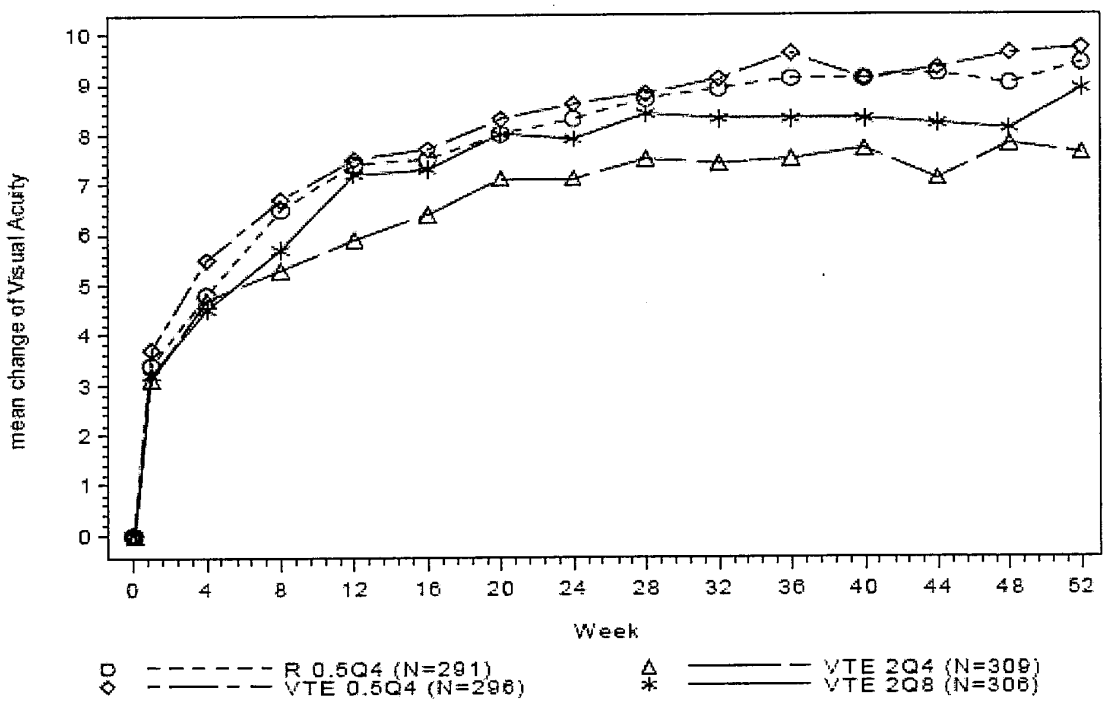
## VIEW #2: Mean ETDRS Letter Score (Full analysis Set with LOCF)

| | 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)



*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)



(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 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]

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

*f. Provide the complete integrated peak area analyses for [redacted] In addition, there are unidentified peaks with percent areas that appear to be greater than [redacted] based on the apparent size of [redacted] 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] and [redacted] 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]

*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] (including [redacted] 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] was "not determined." Clarify this discrepancy.*

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

[redacted] *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] *for DS intermediate, when the proposed acceptance criterion for DS is* [redacted]
   b. *Provide justification for a proposed charge heterogeneity acceptance criterion of* [redacted] *for DS intermediate, when the proposed acceptance criterion for DS is* [redacted]
   c. *Provide justification for the proposed DS protein concentration acceptance criterion* [redacted]
   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] *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]

8. *Regarding reference standard (RS):*
   *Characterization results for the current RS lot* [redacted] *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 (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 (b) (4) and justify the use of (b) (4) during container closure integrity testing. Clarify if step 18.3.2 of batch record document number MR1054, describing (b) (4) is the same as the (b) (4)*
   b. *Justify the use of the (b) (4) leachable/extractable testing (section 3.2.S.6.1.4, Table 2).*
   c. *Clarify the calculation of (b) (4) (3.2.S.6.1.4.2, p. 7), as the FTIR results listed in Table 4 are significantly higher than (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 c (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* (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* (b) (4)

c. *Update the data from the studies assessing effects of* (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* (b) (4) *on stability, section 3.2.P.2.2.1.7.3 states that the control was DP that was "not exposed to* (b) (4) *steel." Clarify this statement; i.e. was DP manufactured without the use of* (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.* (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)

(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]

*ix. The* [redacted] *vial* [redacted] *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] *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)

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)

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(b) (4)

***MICROBIOLOGY/ STERILITY***

1. *The shipping validation information indicates that due to the damage observed after* (b) (4) (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) *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)

(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.

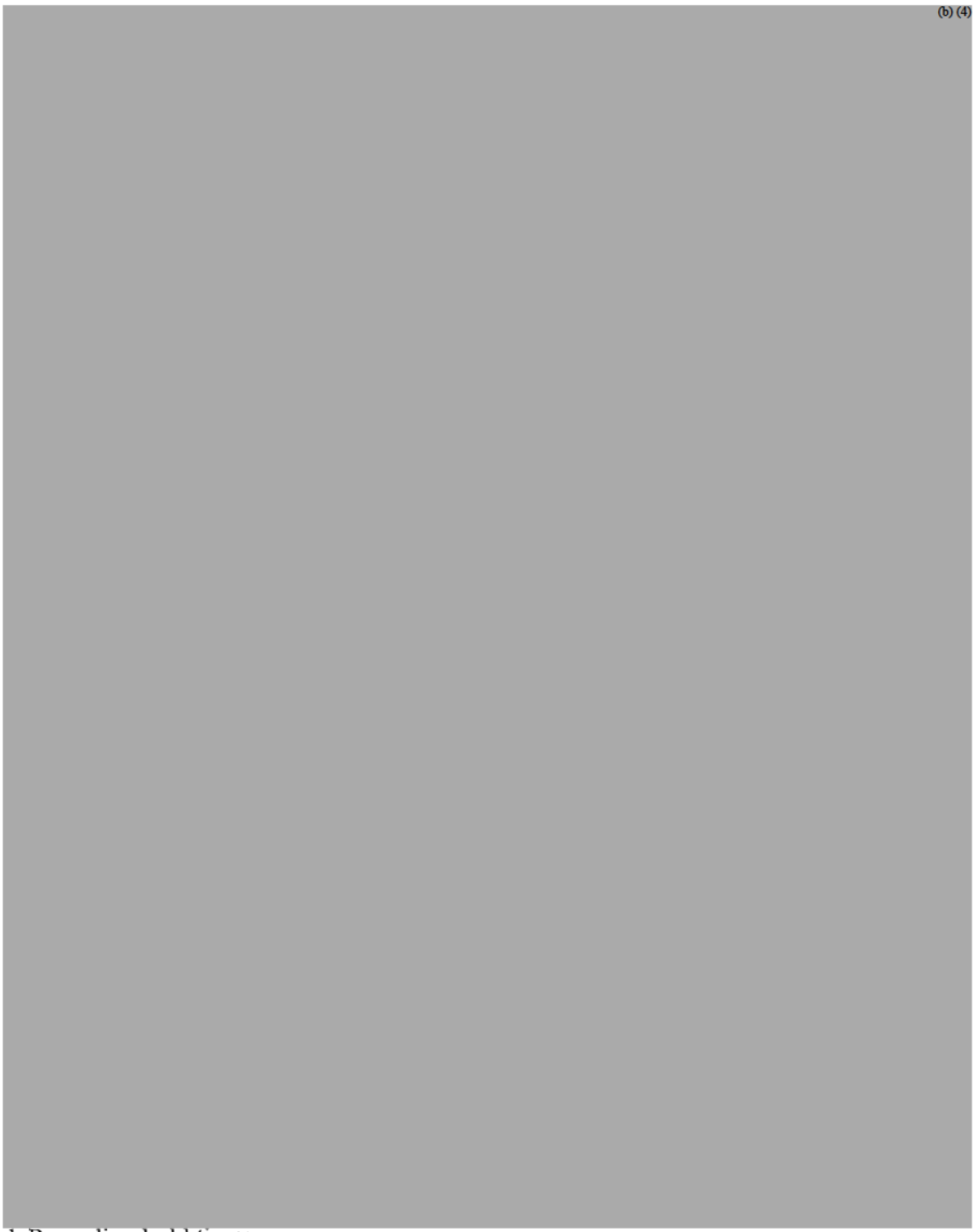
b. For those IPC limits set using historical mean (b) (4) provide justification for setting IPC limits based on (b) (4)

(b) (4)

3. For DS process validation:

(b) (4)

(b) (4)



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 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[redacted]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[redacted]
ii. Provide enlargements of the entire chromatograph[redacted]

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]

e. Provide relative percentage data for [redacted] for each of the lots assessed.

f. Provide the complete integrated peak area analyses for [redacted]. In addition, there are unidentified peaks with percent areas that appear to be greater than [redacted] based on the apparent size of [redacted] 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] and [redacted] 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]

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] (including [redacted] 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] was "not determined." Clarify this discrepancy.
ii. Table 13 lists only 3 N-terminal sequences for the non-reduced [redacted] species [redacted] while an additional sequence with truncation at [redacted] 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]

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] 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] 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] and justify the use of [redacted] during container closure integrity testing. Clarify if step 18.3.2 of batch record document number MR1054, describing [redacted], is the same as the [redacted]
   b. Justify the use of the [redacted] leachable/extractable testing (section 3.2.S.6.1.4, Table 2).
   c. Clarify the calculation of [redacted] (3.2.S.6.1.4.2, p. 7), as the FTIR results listed in Table 4 are significantly higher than [redacted]
   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] and that any failures will

be reported. As drug substance intermediate may be stored for an extended time, it should also [redacted] include all stability data for drug substance and drug substance intermediate in the AR.
b. We note that drug substance stability allows a [redacted] 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] on product quality are not complete. Provide updated data to this section. In addition, provide justification for the filtering of data to exclude [redacted]
c. Update the data from the studies assessing effects of [redacted] 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] on stability, section 3.2.P.2.2.1.7.3 states that the control was DP that was "not exposed to [redacted]" Clarify this statement; i.e. was DP manufactured without the use of [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) 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 (b) (4) (b) (4) the blister pack design will be modified and the shipping validation studies will be repeated.

(b) (4)

(b) (4)

f. [redacted]

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

5. Regarding the cycle development and process validation studies for [redacted]

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

[redacted]

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

[redacted]

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

[redacted]

[redacted]



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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)

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

**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 ..... 4**
1.1 Recommendation on Regulatory Action ..... 4
1.2 Risk Benefit Assessment ..... 4
1.3 Recommendations for Post-marketing Risk Management Activities ..... 4
1.4 Recommendations for other Post-marketing Study Commitments ..... 4
**2 INTRODUCTION AND REGULATORY BACKGROUND ..... 4**
2.1 Product Information ..... 4
2.2 Tables of Currently Available Treatments for Proposed Indications ..... 5
2.3 Availability of Proposed Active Ingredient in the United States ..... 5
2.4 Important Safety Issues With Consideration to Related Drugs ..... 5
2.5 Summary of Pre-submission Regulatory Activity Related to Submission ..... 5
2.6 Other Relevant Background Information ..... 6
**3 ETHICS AND GOOD CLINICAL PRACTICES ..... 6**
3.1 Submission Quality and Integrity ..... 6
3.2 Compliance with Good Clinical Practices ..... 6
3.3 Financial Disclosures ..... 6
**4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES ..... 6**
4.1 Chemistry Manufacturing and Controls ..... 6
4.2 Clinical Microbiology ..... 6
4.3 Preclinical Pharmacology/Toxicology ..... 6
4.4 Clinical Pharmacology ..... 6
4.4.1 Mechanism of Action ..... 6
4.4.2 PK/PD ..... 6
**5 SOURCES OF CLINICAL DATA ..... 6**
5.1 Tables of Clinical Studies ..... 6
5.2 Review Strategy ..... 6
5.3 Discussion of Individual Studies ..... 6
**6 REVIEW OF EFFICACY ..... 6**
6.1 Indication ..... 6
6.1.1 Methods ..... 6
6.1.2 Demographics ..... 6
6.1.3 Patient Disposition ..... 6
6.1.4 Analysis of Primary Endpoint(s) ..... 6
6.1.5 Analysis of Secondary Endpoints(s) ..... 6
6.1.6 Other Endpoints ..... 6
6.1.7 Subpopulations ..... 6
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations ..... 6
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects ..... 6
6.1.10 Additional Efficacy Issues/Analyses ..... 6
**7 REVIEW OF SAFETY ..... 6**
7.1 Methods ..... 6
7.1.1 Clinical Studies Used to Evaluate Safety ..... 6
7.1.2 Adequacy of Data ..... 6
7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence ..... 6
7.2 Adequacy of Safety Assessments ..... 6

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations ..... 6
7.2.2 Explorations for Dose Response ..... 6
7.2.3 Special Animal and/or In Vitro Testing ..... 6
7.2.4 Routine Clinical Testing ..... 6
7.2.5 Metabolic, Clearance, and Interaction Workup ..... 6
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..... 6
7.3 Major Safety Results ..... 6
7.3.1 Deaths ..... 6
7.3.2 Nonfatal Serious Adverse Events ..... 6
7.3.3 Dropouts and/or Discontinuations ..... 6
7.3.4 Significant Adverse Events ..... 6
7.3.5 Submission Specific Primary Safety Concerns ..... 6
7.4 Supportive Safety Results ..... 6
7.4.1 Common Adverse Events ..... 6
7.4.2 Laboratory Findings ..... 6
7.4.3 Vital Signs ..... 6
7.4.4 Electrocardiograms (ECGs) ..... 6
7.4.5 Special Safety Studies ..... 6
7.4.6 Immunogenicity ..... 6
7.5 Other Safety Explorations ..... 6
7.5.1 Dose Dependency for Adverse Events ..... 6
7.5.2 Time Dependency for Adverse Events ..... 6
7.5.3 Drug-Demographic Interactions ..... 6
7.5.4 Drug-Disease Interactions ..... 6
7.5.5 Drug-Drug Interactions ..... 6
7.6 Additional Safety Explorations ..... 6
7.6.1 Human Carcinogenicity ..... 6
7.6.2 Human Reproduction and Pregnancy Data ..... 6
7.6.3 Pediatrics and Effect on Growth ..... 6
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound ..... 6
7.7 Additional Submissions ..... 6

**8 POST-MARKETING EXPERIENCE ..... 6**

**9 APPENDICES ..... 6**

9.1 Literature Review/References ..... 6
9.2 Advisory Committee Meeting ..... 6
9.3 Comments to be sent to Applicant: ..... 6
9.4 Labeling Recommendations ..... 6

# 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)

**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:<br>• 4mg Q4 IVT-1<br>• 4mg Q4 IVT-2<br>• 4mg Q4 open label IVT-2<br><br>After 12 weeks patients received 4mg prn. | 20 | AMD | 12 weeks | Completed |
| VGFT-OD-0502 | 1 | Part A-Phase 1, open-label dose escalation<br><br>Part B-Randomized, double-masked, active controlled<br><br>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).<br><br>VEGF Trap-Eye 2mg prn (PFS)-99 patients<br>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:<br>• 0.5 mg q12 weeks (32 patients)<br>• 0.5 mg q4 weeks for 12 weeks (32 patients)<br>• 2.0 mg q12 weeks (31 patients)<br>• 2.0 mg q4 weeks for 12 weeks (31 patients)<br>• 4.0 mg q12 weeks (31 patients)<br><br>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:<br><br>Ranibizumab q4 weeks (306 patients)<br>VEGF Trap-Eye 2.0 mg q4 weeks (304 patients)<br>VEGF Trap-Eye 0.5 mg q4 weeks (304 patients)<br>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<br>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

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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

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

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

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



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



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

18

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

APPEARS THIS WAY ON ORIGINAL

| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
| (162)<br>New York Eye & Ear Infirmary | 310 East 14th Street<br>South Building, Suite 319<br>New York, NY 10003<br>(212) 979-4251 | Richard Rosen, MD | 2 |
| (153)<br>National Ophthalmic Research Institute | 6901 International Center Boulevard<br>Fort Myers, FL 33912<br>(239) 938-1284 | Joseph P. Walker, MD | 9 |
| (117)<br>New England Retina Associates | 400 Bayonet Street, Suite 206<br>New London, CT 06320<br>(860) 444-1292 | Nauman Chaudhry, MD | 14 |
| (209)<br>Ocala Eye | 3130 SW 32nd Ave<br>Ocala, FL 34474<br>(352) 291-5210 | Chander Samy, MD | 4 |
| (176)<br>Ochsner Clinic Foundation | 1514 Jefferson Highway<br>New Orleans, LA 70121<br>(504) 842-3952 | Laurence Arend, MD | 1 |
| (151)<br>Ophthalmic Consultants of Long Island | 360 Merrick Road, 3rd Floor<br>Lynbrook, NY 11563<br>(516) 593-4026 x251 | Glenn Stoller, MD | 5 |
| (146)<br>Ophthalmic Consultants of Boston | 50 Staniford Street, Suite 600<br>Boston, MA 02114<br>(617) 314-2694 | Jeffrey S. Heier, MD | 32 |
| (148)<br>Ophthalmology Associates | 1201 Summit Avenue<br>Fort Worth, TX 76102-4427<br>(817) 332-2020 | John Parchue, MD | 14 |
| (242)<br>Orange County Retina Medical Group | 1200 North Tustin Avenue, Suite 140<br>Santa Ana, CA 92705<br>(714) 972-8432 | Sanford Chen, MD | 10 |
| (180)<br>Paducah Retinal Center | 1900 Broadway Street, Suite 2<br>Paducah, KY 42001<br>(270) 443-4393 | Carl W. Baker, MD | 2 |
| (145)<br>Palmetto Retina Center, LLC | 124 Sunset Court<br>West Columbia, SC 29169<br>(803) 931-0077 | W. L. Clark, MD | 22 |
| (510)<br>The Medical Center Pasqua Hospital | 1-4101 Dewdney Avenue<br>Regina, Saskatchewan<br>S4TA5, Canada<br>(306) 766-2333 | Raul Garcia, MD | 8 |
| (195)<br>Premier Retina Specialists | 840 Central Drive<br>Odessa, TX 79761<br>(432) 332-2682 | Richard Culbert, MD | 3 |
| (114)<br>Retina Care Specialists LLP | 3399 PGA Boulevard, Suite 220<br>Palm Beach Gardens, FL 33410<br>(561) 624-0099 | Mark Michels, MD | 13 |
| (196)<br>Rocky Mountain Retina | 4400 South 700 East, Suite 200<br>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)<br>Regional Retina | 7330 Fern Avenue, Suite 702<br>Shreveport, LA 71105<br>(318) 798-6699 | David A. Glaser, MD | 5 |
| (274)<br>Retina Associates of St. Louis, Inc. | 1224 Graham Road, Suite 3011<br>Florissant, MO 63031<br>(314) 839-1211 | Ernest Guillet, MD | 11 |
| (165)<br>Retina Associates of Western New York | 160 Sawgrass Drive, Suite 200<br>Rochester, NY 14620<br>(585) 442-3411 | Kenneth Wald, MD | 3 |
| (311)<br>Retina Associates of New York | 140 East 80th Street<br>New York, NY 10021<br>(212) 772-0600 | Kenneth Diddie, MD | 3 |
| (301)<br>Retinal Consultants of Southern California | 1250 La Venta Drive, Suite 208<br>Westlake, CA 91361<br>(805) 379-0200 | Michael Antworth, MD | 13 |
| (220)<br>Retina Consultants of Carolina | 1126 Grove Road<br>Greenville, SC 29605<br>(864) 233-5722 | Darrin Levin, MD | 1 |
| (123)<br>Retina Consultants of Michigan | 29201 Telegraph Road, Suite 606<br>Southfield, MI 48034<br>(248) 356-8610 | Sean Adrean, MD | 3 |
| (284)<br>Retina Consultants of Orange County | 301 West Bastanchury Road, Suite 285<br>Fullerton, CA 92835<br>(714) 738-4620 | James K. Luu, MD | 8 |
| (346)<br>Retina Consultants of Southern Colorado P.C. | 3030 North Circle, Suite 301<br>Colorado Springs, CO 80909<br>(719) 331-7835 | John O. Mason, III, MD | 4 |
| (137)<br>Retina Consultants of Alabama | 700 South 18th Street, Suite 707<br>Birmingham, AL 35223<br>(205) 918-0047 | Murray J. Erasmus, CHB, MB | 39 |
| (505)<br>Retina Consultants of Victoria | 212-911 Yates Street<br>Victoria, British Columbia<br>V8V 1B3, Canada<br>(250) 598-1252 | Pravin U. Dugel., MD | 5 |
| (183)<br>Retinal Consultants of Arizona | 1101 E. Missouri Avenue<br>Phoenix, AZ 85014<br>(602) 222-2221 | Richard Garfinkel, MD | 5 |
| (314)<br>Retina Group of Washington | 8505 Arlington Boulevard, Suite 300<br>Fairfax, VA 22031<br>(703) 698-9335 | Alexander Eaton, MD | 27 |
| (224)<br>Retina Health Center | 1567 Hayley Lane, Suite 101<br>Fort Myers, FL 33907<br>(239) 337-3337 x220 | Tom Chang, MD | 8 |
| (157)<br>Retina Institute of California | 301 W. Huntington Drive, Suite 107<br>Arcadia, CA 91007<br>(626) 568-8838 | | |

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY ON ORIGINAL

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



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



APPEARS THIS WAY ON ORIGINAL

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



APPEARS THIS WAY ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

## 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[1] | | | | | 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[2] | X | X[6] | X | X[2] | X[2] | X | X[2] | X[6] | X | X[6] | X[2] | X[2] | X |
| Fundus Photo/ FA | X[5] | | | | | | | | X | | | | | | | X |
| Hematology & Chemistry Panel[7] | X | | | | | X | | | X | | | X | | | | |
| Serum Beta-HCG | X | | | | | | | | | | | | | | | X |
| PT/PTT[7] | X | | | | | | | | X | | | X | | | | X |
| Urinalysis/UPCR[7] | X | | | | | X | | | X | | | X | | | | X |
| Serum for antibody[7] | X | | | | | X | | | X | | | X | | | | O[11] |
| Study Drug or Sham Injection[8] | | X | | X | X | X[10] | X | X[10] | X | X[10] | X | X[10] | X | X[10] | X | X[9,10] |
| 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[2] | |

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)

APPEARS THIS WAY ON ORIGINAL

**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 | | | | | X | | | | | | X |
| 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

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

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



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| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
| Sapporo City General Hospital | JAPAN<br>Phone: 81-11-726-2211 | Tanaka, Minoru | 16 |
| (20006)<br>Juntendo University Urayasu Hospital | 2-1-1 Tomioka, Urayasu-shi, Chiba 279-0021<br>JAPAN<br>Phone: 81-47-353-3111 | Terasaki , Hiroko | 10 |
| (20007)<br>Nagoya University Hospital | 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560<br>JAPAN<br>Phone: 81-52-741-2111 | Yoshimura, Nagahisa | 8 |
| (20008)<br>Kyoto University Hospital | 54 Kawahara-cho Shogo-in Sakyo-ku, Kyoto 606-8507<br>JAPAN<br>Phone: 81-75-751-3111 | Yuzawa, Mitsuko | 10 |
| (20009)<br>Surugadai Nihon University Hospital | 1-8-13 Surugadai, Kanda, Chiyoda-ku, Tokyo 101-8309<br>JAPAN<br>Phone: 81-3-3293-1711 | Iida, Tomohiro | 10 |
| (20010)<br>Fukushima Medical University Hospital | 1 Hikarigaoka, Fukushima 960-1295<br>JAPAN<br>Phone: 81-24-547-1111 | Ishibashi, Tatsuro | 5 |
| (20011)<br>Kyushu University Hospital | 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582<br>JAPAN<br>Phone: 81-92-641-1151 | Sakamoto, Taiji | 4 |
| (20012)<br>Kagoshima University Medical and Dental Hospital | 8-35-1 Sakuragaoka, Kagoshima 890-8520<br>JAPAN<br>Phone: 81-99-275-5111 | PI - Shiraga, Fumio | 3 |
| (20013)<br>Kagawa University Hospital | 1750-1 Ikenobe Miki-cho, Kagawa 761-0793<br>JAPAN<br>Phone: 81-87-898-5111 | Takahashi, Kanji | 4 |
| (20014)<br>Kansai Medical University Hirakata Hospital | 2-3-1 Shin-mach, Hirakata, Osaka 573-1191<br>JAPAN<br>Phone: 81-72-804-0101 | Gomi, Fumi | 10 |
| (20015)<br>Osaka University Hospital | 2-15 Yamadaoka, Suita, Osaka 565-0871<br>JAPAN<br>Phone: 81-6-6879-5111 | Wagle, Ajeet | 1 |
| (68001)<br>Khoo Teck Puat Hospital | 90 Yishun Central,<br>Singapore (768828)<br>Singapore<br>Phone: 6563793512 | San, Ian Yeo, Y | 7 |
| (68002)<br>Singapore National Eye Centre (SNEC) | 11 Third Hospital Ave Singapore 168751<br>Singapore<br>Phone: 65 9820-6033 | Tan, Nikolle | 4 |
| (68003)<br>Tan Tock Seng Hospital (TTSH) | 11 Jalan Tan Tock Seng Singapore 308433<br>Singapore<br>Phone: 65 6379 3512 | Park, Kyu-Hyung | 4 |
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| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
| (56002)<br>Asan Medical Center Department of Ophthalmology | 3881-1 Pungnap2-dong, Songpagu Seoul 138-736<br>Korea<br>Phone: 82 2 3010 3680 | Yoon, Young-Hee | 9 |
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| (56004)<br>Seoul National University Hospital, Department of Ophthalmology | 101 Daehangno Chongno-gu, Seoul 110-744<br>Korea<br>Phone: 82 2 2072 2438 | Yu, Hyeong-Gon | 5 |
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| (56006)<br>Korea University Guro Hospital Department of Ophthalmology | Guro 2-Dong, Guro-Gu Seoul 152-703<br>Korea<br>Phone: 82 2 2626 1276 | Huh, Kuhl | 1 |
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| (44003)<br>Universitätsklinik für Augenheilkunde und Optomerie Wien<br>Medizinische Universität Wien | Währinger Gürtel 18-20 1090 Vienna<br>Austria<br>Phone: 43 1 40 400 7931 | Schmidt-Erfurth, UrsulaH | 35 |
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| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
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| (16002)<br>Hôpital Lariboisiere service d'ophtalmologie | 2 rue Ambroise Paré 75475 Paris Cedex 10<br>France<br>Phone: 33 (0)1 49 95 24 75 | Gaudric, Alain | 5 |
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| (16007)<br>Centre Ophtalmologique d'Imagerie et de Laser | 11 Rue Antoine Bourdelle 75015 Paris<br>France<br>Phone : 33 (0)1 42 84 94 00 | Quentel, Gabriel | 8 |
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| (10002)<br>Universitäts-Augenklinik Freiburg | Killianstr. 5<br>79106 Freiburg<br>Germany<br>Phone: 49 761 2704013 | Hansen, Lutz, L | 15 |
| (10005)<br>Augenambulanz | Hohenzollernring 72<br>48145 Münster<br>Germany<br>Phone: 49 251 935-0 +49 251 935-462 | Pauleikhoff, Daniel | 1 |
| (10006) | Martinistrasse 52 | Richard, Gisbert | 5 |



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| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
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| (10007)<br>Universitätsklinikum Kiel Klinik für Augenheilkunde | Hegewischstrasse 2 24105 Kiel<br>Germany<br>Phone: 49 431 5974834 | Roider, Johann | 4 |
| (10008)<br>Augenklinik Charite Campus - Benjamin Franklin | Hindenburgdamm 30 12200 Berlin<br>Germany<br>Phone: 0049 30 450 554 001 | Foerster, Michael, H | 1 |
| (10009)<br>Universitätsklinikum Leipzig AöR Klinik und Poliklinik für Augenheilkunde | Liebigstr. 10-14<br>04103 Leipzig<br>Germany<br>Phone: 49 341 9721650 | Wiedemann, Peter | 7 |
| (10010)<br>Universitäts-Augenklinik | Bonn Ernst-Abbe-Str.2 53127 Bonn<br>Germany<br>Phone: 49 228 28715647 | Holz, Frank, G | 10 |
| (10012)<br>Klinikum rechts der Isar Augenklinik | Ismaninger Str. 22<br>81675 München<br>Germany<br>Phone: 49(0)894140-2320 | Lohmann, Chris, P | 11 |
| (10013)<br>Universitäts-Augenklinik Mainz | Langenbeckstr. 1<br>55131 Mainz<br>Germany<br>Phone: 49 6131 177085 | Pfeiffer, Norbert | 10 |
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| (10015)<br>Universitätsklinikum Essen Zentrum für Augenheilkunde | Hufelandstr. 55<br>45122 Essen<br>Germany<br>Phone: 49 201 723 3568 | Bornfeld, Norbert | 2 |
| (10017)<br>Universitätsklinikum Heidelberg Augenklinik | Im Neuenheimer Feld 400 69120<br>Heidelberg<br>Germany<br>Phone: 49 6221 56 6695 | Dithmar, Stefan | 7 |
| (10019)<br>Klinik und Poliklinik für Augenheilkunde am Universitätsklinikum Carl Gustav Carus | Fetscherstraße 74<br>01307 Dresden<br>Germany<br>Phone: 49 351 458 5104 | Sandner, Dirk | 3 |
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| (10024)<br>Krankenhaus Dresden | Friedrichstr. 41<br>01067 Dresden<br>Germany | Hachs, Helmut, G | 3 |



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| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
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| (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 |
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| (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 |



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| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
| | Phone : 972-57-7345362 | | |
| (39008)<br>Meir Medical Center,<br>Ophthalmology Department | Kfar Saba , 95847<br>Israel<br>Phone : 972 9 7472776 | Ferencz, Joseph | 6 |
| (39010)<br>Carmel Medical Center<br>Ophthalmology Clinic | Haifa 34362,<br>Israel<br>Phone: 972 4 8250419 | Mathalone, Nurit | 5 |
| (22002)<br>Azienda Ospedaliera Ospedale Consorziale e Policlinico<br>Università degli Studi<br>Dipartimento di Oftalmologia | Piazza Giulio Cesare, 11 70124 Bari<br>Italy<br>Phone: 0039 080 5594027 | Boscia, Francesco | 1 |
| (22004)<br>Fondazione G.B. Bietti-IRCCS<br>Divisione di Retina Medica | via Livenza 3<br>00198 Roma<br>Italy<br>Phone: 0039 06 85356727 | Varano, Monica | 8 |
| (22006)<br>Ospedale San Martino Isituto<br>Clinica Oculistica | Viale Benedetto XV, 5 16132 Genova<br>Italy<br>Phone: 0039 01035338322 | Ghiglione, Davidina | 6 |
| (22009)<br>Ospedali Riuniti Umberto I- GM Lancisi-G. Salesi Università di Ancona U.O. Clinica Oculistica | Via Conca, 71<br>60020 Torrette di Ancona<br>Italy<br>0039 071 5964381 0039 071 5964391 | Giovannini, Alfonso | 7 |
| (22012)<br>Opsedale Luigi Sacco<br>Dipartimento di Scienze Cliniche<br>Università di Milano | via G.B. Grassi, 74<br>20157 Milano<br>Italy<br>Phone: 0039 02 39042901 | Staurenghi, Giovanni | 16 |
| (22013)<br>Ospedale Maggiore Policlinico Mangiagalli, Regina Elena-IRCCS U.O. di Oculistica | via M fandi<br>20122 Millano<br>Italy<br>Phone: 0039 02 50320844 | Viola, Francesco | 9 |
| (22014)<br>Ospedale di Circolo Fondazione Macchi U.O. di Oculistica | viale Borri, 57<br>21100 Varese<br>Italy<br>Phone: 0039 0332278217 | Azzolini, Claudio | 1 |
| (22015)<br>Ospedale Oftalmico Clinica Oculistica<br>Università degli Studi | via Juvarra, 19<br>10122 Torino<br>Italy<br>Phone: 0039 011 5666185 | Grignolo, Frederico | 2 |
| (22016)<br>Ospedale San Raffaele IRCCS<br>Unità Operativa di Oculistica | via Olgettina 60<br>20132 Milano<br>Italy<br>Phone: 0039 26432645 | Introini, Ugo | 5 |
| (22018)<br>Azienda Ospedaliero Universitaria- Policlinico "G. Rodolico" U.O. di Oculistica | Via S.Sofia 78<br>95123 Catania<br>Italy<br>Phone: 0039 0953781095 | Reibaldi, Alfredo | 3 |
| (22020)<br>Policlinico tor Vergata Centro di | viale Oxford, 81<br>00133 Roma | Ricci, Federico | 21 |

| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
| Riferimento Regionale per la Diagnosi e la Terapia delle Degenerazione Maculare senile e delle Patologie Retiniche Cecitanti, | Italy<br>Phone: 0039 06 20903579 | | |
| (76001)<br>Paula Stradiņa Klīniskās Universitātes slimnīca Oftalmoloģijas nodaļa, | Pilsoņu iela 13,<br>Rīga, 1002,<br>Latvia<br>Phone: 371 29106879 | PI - Laganovska, Guna | 18 |
| (76003)<br>Latvijas-Amerikas acu centrs | Tallinas iela 93<br>Rīga, 1009<br>Latvia<br>Phone: 371 29282917 | Zarinova, Ilze | 13 |
| (30001)<br>Leiden University Medical Center Department of Opthalmolgy | Albinusdreef 2<br>2333 ZA Leiden<br>The Netherlands<br>Phone: 0031 71 526 30 84 | Dijkman, G. | 6 |
| (30002)<br>University Medical Center St. Radboud Department of Opthalmology | Philips van Leydenlaan 15 6525 EX<br>Nijmegen<br>The Netherlands<br>Phone: 0031 24 361 31 38 | Hoyng, Carel, B | 13 |
| (30004)<br>Erasmus MC<br>Department of Ophthalmology | PO Box 2040<br>3000 CA Rotterdam 's Gravendijkwal 230<br>3015 CE Rotterdam<br>The Netherlands<br>Phone: 0031 10 463 36 91 | Vingerling, Hans, R | 6 |
| (30006)<br>University Medical Center Groningen Department of Ophthalmology | PO BOX 30.001 9700 RB Groningen<br>Hanzeplein 1 9713 GZ Groningen<br>The Netherlands<br>Phone: 0031 10 463 36 91 | Hooymans, J., M | 2 |
| (18002)<br>Szpital Kliniczny Dzieciątka Jezus Centrum Leczenia Obrażeń Klinika Okulistyki ul | Lindleya 4;<br>02-005 Warszawa<br>Poland<br>Phone: 48225021554 | Kecik, Dariusz | 3 |
| (18003)<br>Szpital Kliniczny Przemienienia Pańskiego Uniwersytetu Medycznego im Karola Marcinkowskiego w Poznaniu Katedra i Klinika Okulistyki | Ul. Długa ½;<br>61-848 Poznań<br>Poland<br>Phone: 48618549284 | Kociecki, Jaroslaw, | 5 |
| (18004)<br>Klinika Okulistyki Samodzielnego Publicznego Szpitala Klinicznego nr 1 we Wrocławiu | ul. Chałubińskiego 2a<br>50-368 Wrocław<br>Poland<br>Phone: 48717842427 | Misiuk-Hojlo, Marta | 10 |
| (18006) | ul. Dębinki 7<br>80-952 Gdańsk | Raczynska, Krystyna | 7 |



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| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
| Akademickie Centrum Kliniczne Szpital Akademii Medycznej w Gdańsku Klinika Chorób Oczu | Poland<br>Phone: 48583492370 | | |
| (18009)<br>Okręgowy Szpital Kolejowy w Katowicach<br>S.P.Z.O.Z. Oddział Okulistyczny | Ul.Panewnicka 65;<br>40-760 Katowice<br>Poland<br>Phone: 48323530856 | Wylegala, Edward | 12 |
| (18011)<br>Niepubliczny Zakład Opieki Zdrowotnej „OFTALMIKA" | Ul. Modrzewiowa 15<br>85-631 Bydgoszcz<br>Poland<br>Phone: 48604226747 | Kaluzny, Jozef | 6 |
| (42002)<br>**Hospital de São Joao, EPE**<br>Serviço de Oftalmologia<br>Alameda Prof. Hernani | Monteiro<br>4200-319 Porto<br>Portugal<br>Phone: 225507103 | Carneiro, Ângela | 3 |
| (42003)<br>AIBILI | Azinhaga de Santa Comba - Celas<br>3000-548 Coimbra<br>Portugal | Martins da Silva, Rufino | 13 |
| (52001)<br>2.očná klinika<br>Fakultná Nemocnica F.D. Roosevelta, | Nam. L. Svobodu 1,<br>97517 Banská Bystrica<br>Slovakia<br>Phone: 00421915831415 | Izak, Milan | 13 |
| (52002)<br>Očná klinika<br>Fakultná nemocnica s poliklinikou, | Ružinovská 6,<br>821 06 Bratislava<br>Slovakia<br>Phone:00421905238050 | Strmen, Peter | 5 |
| (24001)<br>Instituto Clínico de Oftalmología (Hospital Clinic i provincial de Barcelona) Casa maternitat | C/ Sabino Arán s/n, Área médico-administrativa 2° piso, 08028 Barcelona<br>Spain<br>Phone: 0034 93 227 56 11 | Adán, Alfredo | 2 |
| (24003)<br>IOBA-Instituto de Oftalmobiología Aplicada<br>Campus Miguel Delibes | Camino del cementerio s/n<br>47011 Valladolid<br>Spain<br>Phone: 0034 983 184 734 | Coco, Rosa María | 1 |
| (24004)<br>Hospital General Universitario de Valencia<br>Servicio de Oftalmología | Avda. Tres Cruces, s/n 46014 – VALENCIA<br>Spain<br>Phone: 0034 96 197 20 00 | Cervera, Enrique | 5 |
| (24005)<br>Hospital Universitario Virgen Macarena<br>Servicio de Oftalmología | Avda. Dr. Fedriani, s/n 41009 SEVILLA<br>Spain<br>Phone: 0034 95 500 91 82 | Esteban González, Eduardo | 1 |
| (24006)<br>Instituto Tecnológico de Oftalmología Hospital | Nuestra Señora de la Esperanza Avda. de las Burgas, 2 15705, Santiago de Compostela La Coruña<br>Spain<br>Phone: 0034 981 585733 | Gomez-Ulla, Francisco | 4 |
| (24007) | Avda. de Denia, s/n, Edif. Vissum 03016 | Ruiz Moreno, José María | 6 |

| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
| Vissum Corporacion Alicante | Alicante<br>Spain<br>Phone: 0034 965154062 | | |
| (24009)<br>VISSUM Hospital Oftalmológico Madrid | C/ Santa Hortensia, 58 28002 - Madrid<br>Spain<br>Phone: 0034 91 510 66 35 | Alvarez Garcia, Maria Teresa | 5 |
| (24012)<br>Instituto Oftalmologico Fernandez Vega Avda | Dres. Fernández-Vega, n 33012 OVIEDO<br>Spain<br>Phone: 0034 985 24 01 41 | Alfonso, Jose Fernando | 4 |
| (24013)<br>Clinica Universidad de Navarra Servicio de Oftalmología Avda | Pío XII, 36 31008 - PAMPLONA<br>Spain<br>Phone: 0034 948 29 63 31 | Garcia Layana, Alfredo | 2 |
| (24014)<br>Hospital Vall d'Hebrón Servicio de Oftalmología | Passeig de la Vall d'Hebrón, 119-129<br>08035 Barcelona<br>Spain<br>Phone: 0034 93 489 30 00 | Garcia-Arumi, Jose | 1 |
| (24015)<br>Instituto Universitario Dexeus Instituto Oftalmológcio de Barcelona | Avda. Diagonal 632 08017 Barcelona<br>Spain<br>Phone: 0034 93 241 91 00 | Sararols, Laura | 14 |
| (24018)<br>Clínica Piñero Glorieta Plus Ultra | 1 41013 - Sevilla<br>Spain<br>Phone: 0034 954296543 | Pinero, Antonio | 1 |
| (24019)<br>Hospital General de Malaga - Carlos Haya (Hospital Civil) Servicio de Oftalmología | Plaza del Hospital Civil s/n 29009 - MALAGA<br>Spain<br>Phone. 0034 951 29 03 36 | Hernando, Carlos | 4 |
| (24024)<br>FOM Fundacion Oftalmológica del Mediterraneo Bifurcación Pío Baroja | General Avilés, s/n<br>46015 VALENCIA<br>Spain<br>Phone: 0034 96 232 81 23 | Navea, Amparo | 3 |
| (24027)<br>Institut de la Macula I de la Retina Centro Medico Teknon Consultoris Vilana | Area desp 117 C/ Vilana 12 08022, Barcelona<br>Spain<br>Phone: 0034 933 933 117 | Basauri, Ernesto | 3 |
| (34003)<br>Linköping University Hospital Eye Clinic | Entrance 26<br>Linköping, 58185<br>Sweden<br>Phone: 004613222340 | Frennesson, Christina | 2 |
| (34004)<br>Örebro University Hospital Eye Clinic | House A<br>Orebro, 701 85<br>Sweden<br>Phone: 46 19 6022601 | Johansson, Ingrid | 3 |
| (58002)<br>UniversitätsSpital Zürich Augenklinik | Frauenklinikstr. 24<br>8091 Zürich<br>Switzerland<br>Phone: 41-44-255 4949 | Kurz-Levin, Malaika | 5 |
| (58003) | Rue Alcide-Jenther 22 1211 Genève<br>Switzerland | Pournaras, Constantin, J | 3 |



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| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
| Clinique dÓphtalmologie de Genève<br>Hop. Cantonal Universitaire de Gèneve | Phone: 41 22 382 8400 | | |
| (58004)<br>Universitätsspital Basel<br>Augenklinik | Mittlere Str. 91<br>4031 Basel<br>Switzerland<br>Phone: 41 61 265 86991 | Schneider, Ulrike | 2 |
| (58005)<br>Universitätsspital Bern Klinik und Poliklinik für Augenheilkunde<br>Inselspital | 3010 Bern<br>Switzerland<br>Phone: 41 31632 8503 | Wolf, Sebastian | 2 |
| (12004)<br>St. Paul's Eye Research Centre<br>Royal Liverpool University Hospital, | Prescot St,<br>Liverpool, L7 8XP<br>United Kingdom<br>Phone: 0151 706 3977 | Briggs, Michael, C | 3 |
| (12005)<br>Department of Ophthalmology<br>King's College Hospital | Denmark Hill<br>London SE5 9RS<br>United Kingdom<br>Phone: 020 3299 4548 | Sivaprasad, Sobha | 2 |
| (12007)<br>Western Eye Hospital | Marylebone Road,<br>London NW1 5QH<br>United Kingdom<br>Phone: 44 20-7886-7724 | George, Sheena | 4 |
| (12008)<br>Aberdeen Royal Infirmary<br>Ophthalmology Department | Foresterhill<br>Aberdeen AB25 2ZN<br>United Kingdom<br>Phone: 01224 553217 | Lois, Noemi | 4 |
| (12009)<br>Southampton Eye Unit<br>Southampton General Hospital | Tremona Road<br>Southampton,<br>Hampshire, SO16 6YD<br>United Kingdom<br>Phone: 02380 798738 | Lotery, Andrew | 2 |
| (12010)<br>Royal Victoria Hospital | Ward 27, ENT Building<br>Grosvenor Road<br>Belfast BT12 6BA<br>United Kingdom<br>Phone: 02890 632527/2729 | Chakravarthy, Usha | 3 |
| (12011)<br>South Devon Healthcare NHS Foundation Trust<br>Torbay Hospital | Lawes Bridge,<br>Torquay, TQ2 7AA<br>United Kingdom<br>Phone: 0044 1803654830 | Cole, Mick | 4 |
| (12015)<br>Frimley Park Hospital NHS Foundation Trust | Portsmouth Road Frimley Surrey GU16 7UJ<br>United Kingdom<br>Phone: 0044 (0)1276604838 | Menon, Geeta | 5 |
| (12016)<br>Royal Eye Infirmary Plymouth Hospitals NHS Trust | Apsley Road<br>Plymouth PL4 6PL<br>United Kingdom<br>Phone: 447720718667 | Raman, Vasant | 3 |
| (12017) | Aston Triangle, Birmingham B4 7ET.<br>United Kingdom | Gibson, Jonathan, M | 3 |

| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
| Academic Unit of Ophtalmology<br>Aston Academy of Life Sciences<br>Aston University | Phone: 0044 121 2043851 | | |
| (43001)<br>Oftalmólogos especialistas | Urquiza 1288 Rosario.<br>Argentina<br>Phone: 54 341 4110295 | Bafalluy, Joaquin, A | 5 |
| (43004)<br>Inst. Oftalmológico de Córdoba<br>Privado | Boulevard Chacabuco 879,<br>X5000IIT Córdoba, Argentina<br>Phone: (549351) 6662226 | Tacite, Domingo | 2 |
| (43006)<br>Fundación Zambrano | Callao 1046 1o A C1023AAQ Buenos Aires<br>Argentina<br>Phone: (5411) 4813-1919 / 1916 | Zambrano, Alberto, D | 7 |
| (43010)<br>Organización Médica de Investigación (OMI) | Uruguay 725, PB. C1015ABO Ciudad Autónoma de Buenos Aires<br>Argentina<br>Phone: (5411) 4372-0308 | Schlottmann, Patricio, G | 25 |
| (50001)<br>Hospital das Clínicas<br>Faculdade de Medicina de Ribeirão | Preto-USP-Av.Bandeirantes 3900, Unidade de Pesquisa Clínica, Monte Alegre, Ribeirão<br>Brazil<br>Phone: 55 16 3602 2528 | Messias, André Márcio, V | 2 |
| (50003)<br>Escola Paulista de Medicina<br>Hospital São Paulo | Rua Loefgreen, 1726 - São Paulo - SP CEP: 04040-002<br>Brazil<br>Phone: 55 11 55726443 | Belfort Mattos, Rubens | 4 |
| (50005)<br>Instituto da Visão Rua dos Otoni | 881, Floor 13, Santa Efigênia, Minas Gerais CEP: 30150-270<br>Brazil<br>Phone: 55 31 3274-3355 | Nehemy, Marcio, B | 6 |
| (48002)<br>Clínica de Oftalmologia San Diego | Cra. 43 #<br>30-28 Medellín<br>Colombia<br>Phone: 57-4-2626741 | Arango, Santiago | 21 |
| (48004)<br>Clinica de Oftalmologia de Cali | cra.47 sur # 8C-94 Cali<br>Colombia<br>Phone: 57-2-5110259 | Ocampo, Hugo, H | 8 |
| (48006)<br>Fundacion Oftalmologica Nacional | Calle 50 #<br>13-50 Bogotá<br>Colombia<br>Phone: 57-1-3451754 | Rodriguez, Francisco, J | 13 |
| (48007)<br>Instituto Nacional de Investigación en Oftalmología | Cra 48 # 19 A 40 Floor 12 Office 1221<br>Torre Médica Ciudad del Río<br>Colombia<br>Phone: 57-4-3111421 ext. 112 | Sanchez, Juan, G | 19 |
| (32001)<br>Instituto de Oftalmologia Fundación de Asistencia | Privada Conde de Valenciana I.A.P<br>Chimalpopoca 14 Col. Obrera06800<br>Mexico City,<br>Mexico<br>Phone: 52(55)54421704 | Cano Hidalgo, Rene | 1 |
| (32002)<br>Servicio de Oftalmología | Avenida Francisco I. Madero y Gonzalitos s/n, Col. Mitras Centro, C.P. 64460<br>Mexico | Mohamed, Karim | 5 |



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| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Randomized Subjects |
|---|---|---|---|
| Hospital Universitario "Dr. Jose Eleuterio Gonzalez" | Phone: (+52) 81 83 46 06 19 | | |
| (32005)<br>Hospital CIMA | Haciendas del Valle 7120 Fraccionamiento Plaza las Haciendas, CP 31238, Chihuahua, Mexico<br>Phone: 52 (61) 44 39 86 06 | Gomez, Adriana, I | 3 |
| (32006)<br>Centro Oftalmologico de Guadalajara | S.A. de C.V. Avenida Prolongacion Americas 1200 Col. Altamira 45160<br>Zapopan, Jalisco. Mexico<br>Phone: 52(33)38337373 | Padilla Ailhaud, Andres | 6 |
| (32008)<br>Asociacion Para Evitar la Ceguera en Mexico IAP | Hospital Dr. Luis Sanchez Bulnes Vicente Garcia Torres # 46 Col. San Lucas<br>Coyoacan CP 04030 Mexico DF<br>Phone: 52 55 10 84 14 00 ex.t 1171 | Morales Canton, Virgilio | 6 |
| (32009)<br>Oftalmolaser de Monterrey Hidalgo | #2425 Penthouse 1102 Col. Obispado. C.P. 64030 Monterrey, Nuevo León.<br>Mexico<br>Phone: 52(81)83186767 | Del Valle Cantu, Javier | 8 |

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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 | | | | | | | | | | | | | | | X |
| Vital signs (temperature, blood pressure and pulse) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[1] |
| NEI VFQ-25[1] | X[1] | | | | | X[1] | | | X[1] | | | X[1] | | | | X |
| 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 | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| IOP | 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 |
| 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 | | | X | | | | X |
| DNA blood sampling (optional) | | X[10] | | | | X | | | | | | | | | | |
| Hematology & chemistry panel[4] | X | | | | | | | | X | | | X | | | | |
| Serum pregnancy test | X | | | | | | | | | | | | | | | 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[9] | | | | | | | | | | | | | | O[9] |
| PK blood sampling prior to injection | | X[11] | X | X | | X | X | X[8] | X | X[8] | X | X[8] | X | X[8] | X | X[5,8] |
| Study drug or sham injection[7] | | X | | X | X | X[8] | X[9] | X[8] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | |
| Telephone safety check[5] | | X | | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | X[5] | |

| 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 | | | | | | |
| Serum for antibody[4] | | | | | | | | | | | |
| PK blood sampling prior to injection | X[10] | | | | | | | | | | |
| 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] | X |
| End of study | | | | | | | | | | | |

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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). Telephone safety check is still required if no injection was administered.
10 If optional injection is performed the telephone safety check must be completed.
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 8 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 96.

**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

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- 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 |



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## 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 |



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| | | | | |
|---|---|---|---|---|
| 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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### 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) |

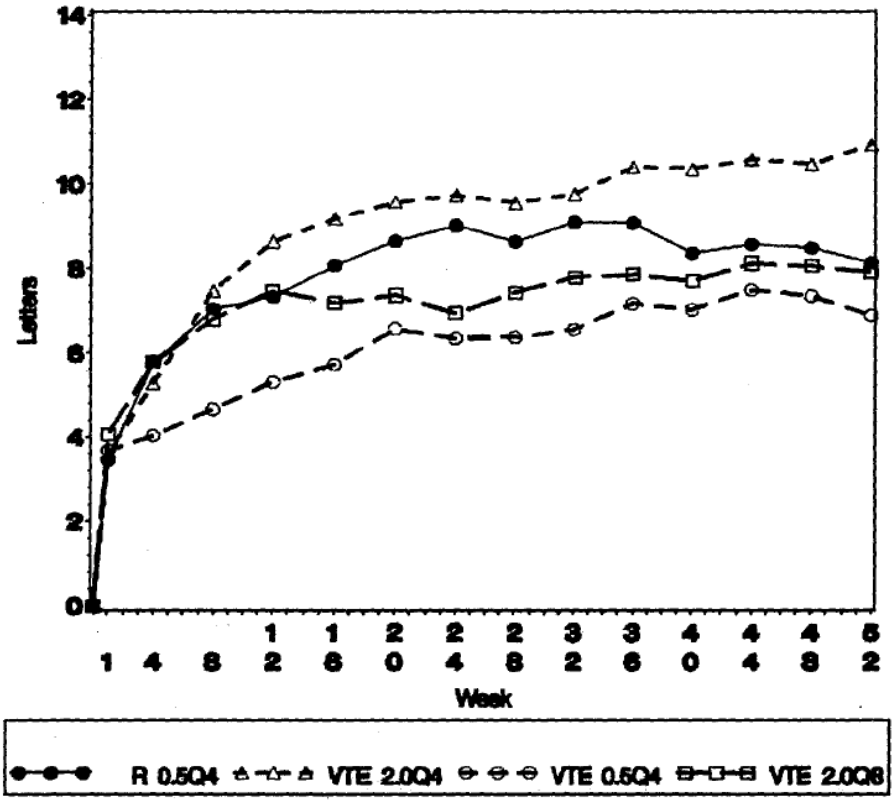
## VIEW #1: Mean ETDRS Letter Score (Full analysis Set with LOCF)

| | 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)**



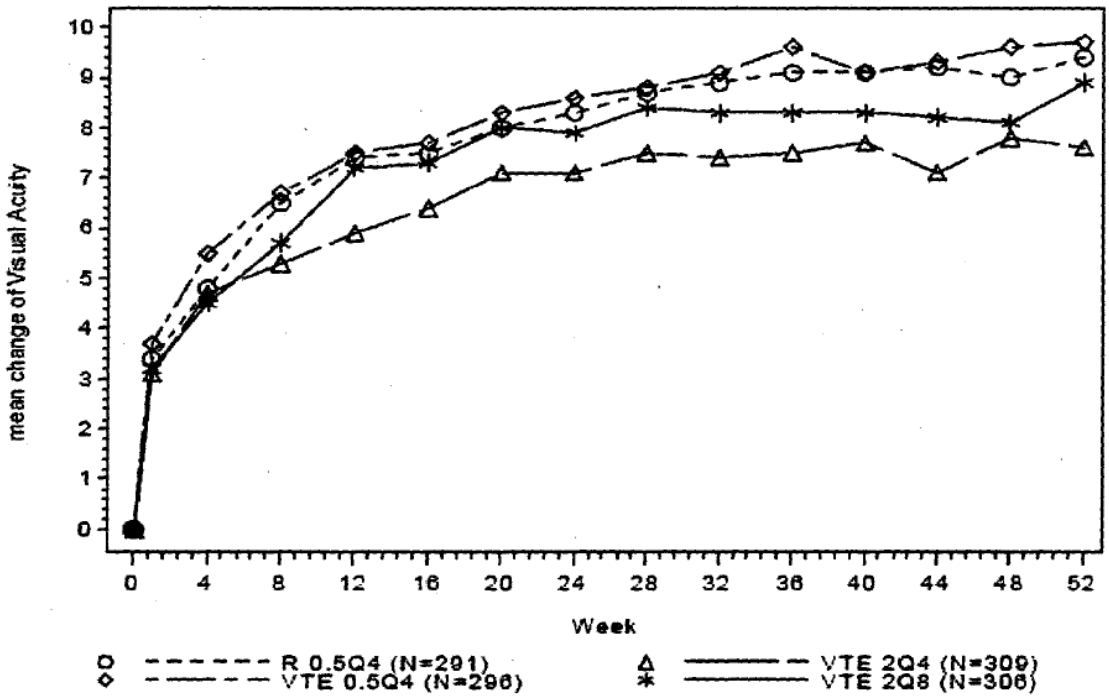
## VIEW #2: Mean ETDRS Letter Score (Full analysis Set with LOCF)

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

| (Site Number) Name of Study Site | Location/Address | Principal Investigator | Number of Enrolled Subjects |
|---|---|---|---|
| (007)<br>Loma Linda University Health Care | 11370 Anderson Street , Suite 1800<br>Loma Linda, CA 92354<br>909-558-2168 | Joseph Fan, MD | 3 |
| (013)<br>Retina Vitreous Associates Medical Group | 8641 Wilshire Blvd , Suite 210<br>Beverly Hills, CA 90211<br>310-289-2478 | David S. Boyer, MD | 6 |
| (015)<br>National Ophthalmic Research Institute | 6901 International Center Blvd.<br>Ft. Myers, FL 33912<br>239-938-1284 | Joseph Walker, MD | 2 |
| (018)<br>Southeast Retina Center | 3685 Wheeler Road, Suite 201<br>Augusta, GA 30909<br>706-650-0061 | Dennis Marcus, MD | 10 |
| (019)<br>NorthShore University HealthSystems | 2050 Pfingsten Road ,Suite 280<br>Glenview IL 60026<br>847-657-1860 | Aaron Weinberg, MD | 1 |
| (020)<br>Ophthalmic Consultants of Boston | 50 Staniford Street ,Suite 600<br>Boston, MA 02114<br>Ph: (617)-367-4800 | Jeffrey Heier, MD | 8 |
| (# 022)<br>Retina-Vitreous Center | 530 Lakehurst Rd.,Suite 305<br>Toms River, NJ 08755<br>732-797-3984 | Daniel Roth, MD | 6 |
| (025)<br>Retina Consultants of Houston, P.A. | Texas Medical Center, Scurlock Tower<br>6560 Fannin #750<br>Houston, TX 77030<br>713-524-3434 | Matthew Benz, MD | 10 |
| (026)<br>Retina Northwest PC | 2525 NW Lovejoy, Suite 300<br>Portland OR 97210<br>503-274-2121 | Michael Lee, MD | 2 |
| (027)<br>Center for Retina and Macular Disease | 250 Avenue K, SW<br>Winter Haven FL 33880<br>863-297-5400 | Michael Tolentino, MD | 10 |
| (028)<br>Black Hills Regional Eye Institute | 2800 Third Street<br>Rapid City SD 57701<br>605-341-2000 | Prema Abraham, MD | 15 |
| (029)<br>Midwest Eye Institute | 200 W. 103rd Street, Suite 1050<br>Indianapolis, IN 46290<br>317-805-2179 | Thomas Ciulla, MD | 7 |
| (030)<br>Associated Retina Consultants | 7600 North 15th Street, Suite 155<br>Phoenix, AZ 85020<br>602-242-4928 x 115 | Clive Sell, MD | 2 |
| (032)<br>New England Retina Consultants PC | 3640 Main Street, Suite 201<br>Springfield, MA 01107<br>413-732-2333 | Brad Foster, MD | 2 |
| (034)<br>So. California Desert Retina Consultants | 36949 Cook Street, Suite 101<br>Palm Desert, CA 92211<br>760-327-6225 | Clement Chan, MD | 2 |
| (035)<br>Medical Center Ophthalmology | 9157 Huebner Road<br>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)<br>Rocky Mountain Retina Consultants | 4400 South, 700 East, Suite 200<br>Salt Lake City, UT 84107<br>801-264-4444 | David Faber, MD | 2 |
| (040)<br>Retinal Consultants of Southern California | 1250 La Venta Drive, Suite 208<br>Westlake Village, California 91361<br>805-379-0200 | Kenneth R. Diddie, MD | 1 |
| (043)<br>East Florida Eye Institute | 509 SE Riverside Dr., Suite 302<br>Stuart, FL 34994<br>772-287-9000 | Ronald E. Frenkel, MD | 1 |
| (044)<br>Retina Institute of California | 301 W. Huntington Drive, Suite 107<br>Arcadia, CA 91007<br>626-568-8838 | Tom Chang, MD | 1 |
| (045)<br>Ophthalmology Associates | 1201 Summit Avenue<br>Fort Worth, TX 76102<br>817-332-2020 | John A. Parchue, MD | 3 |
| (046)<br>Retina Consultants San Diego | 12630 Monte Vista Road, Suite 104<br>Poway, CA 92064<br>858-451-1911 | Paul Tornambe, MD | 4 |
| (047)<br>Retina Research Center | 3705 Medical Parkway, Suite 420<br>Austin, TX 78705<br>512-454-0138 | Brian Berger, MD | 3 |
| (048)<br>Ophthalmic Consultants of Long Island (OCLI) | 360 Merrick Road, 3rd Floor<br>Lynbrook, NY 11563<br>516 593-4026 | Glenn Stoller, MD | 4 |
| (049)<br>Retina Health Center | 1567 Hayley Lane<br>Fort Myers, FL 33907<br>Ph: 239-337-3337 | Alexander Eaton, MD | 4 |
| (050)<br>Palmetto Retina Center | 124 Sunset Court<br>W. Columbia, SC 29169<br>803-931-0077 | John A. Wells, III, MD | 1 |
| (051)<br>Valley Retina Institute | 1309 East Ridge Road, Suite 1<br>McAllen, TX 78503<br>956-631-8875 | Victor Gonzalez, MD | 2 |
| (052)<br>Cumberland Valley Retina Consultants, PC | 1150 Opal Court<br>Hagerstown, MD 21740<br>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[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | 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[g] | 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[g] | X[f] | | | X[f] | | | X[f] | | | X[f] | | | X[f] | | | X[f] | | | X[f] | | X[f] |
| VEGF Trap-Eye Injection[h,i,k] | O[e,g] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | O[e] | |
| 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.

## Study Schedule for Optional Visits

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| 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[f] | X[f] |
| Prot Refraction/VA (ETDRS) | X | X |
| Hematology & Chemistry Panel[e] | | |
| Urinalysis[e] | | |
| Serum for antibody[e] | | |
| VEGF Trap-Eye Injection[g,h,i] | 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 fibroxanthoma | 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 Sonal D. Wadhwa 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?<br><br>~~Study #1: VIEW 1~~<br>Indication: Wet AMD<br><br>Study #2: VIEW 2<br>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) ecause 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