CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products[1]
Subject	Division Director Summary Review
BLA Number	BLA 125387
Related INDs	IND 12462 for wet age-related macular degeneration (b) (4)
Other IND	IND (b) (4) IND (b) (4)
Applicant Name	Regeneron Pharmaceuticals Inc
Date of Submission **Date of Receipt**	February 17, 2011 February 18, 2011
PDUFA Goal Date	August 18, 2011
Major Amendment	August 12, 2001
Revised PDUFA Goal Date	November 18, 2011
Proprietary Name / **Established (USAN) Name**	Eylea™ aflibercept
Formulation **Dose**	(Ophthalmic) intravitreal injection 2 mg in 0.05 mL (40 mg/mL solution) in one single-use glass vial containing 0.278 mL of 40 mg/mL aflibercept ((b) (4) vial)
Proposed Indication(s)	Treatment of patients with neovascular (wet) age-related macular degeneration (AMD)
Action for NME	*Approval*

[1] The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sonal Wadhwa, Bill Boyd, Wiley Chambers 7/2011
CDTL Review	Bill Boyd
Deputy Director	Wiley Chambers
Statistical Review	Dongliang Zhuang, Yan Wang, Mohammed Huque 7/2011
Pharmacology/Toxicology Review	Maria Rivera, William Taylor 7/2011
Clinical Pharmacology Review	Yongheng (Eric) Zhang, Philip Colangelo 7/2011
Product Quality Reviews OPS/OBP/DMA	Sarah Kennett, Sang Bong Lee, Chana Fuchs, Patrick Swann, Kathleen Clouse 11/10/2011
Quality Microbiology Reviews OC/OMPQ/DGMPA/BMAB	Reyes Candau-Chacon, Colleen Thomas, Kala Suvarna, Patricia Hughes 10/11/2011
OC/Facilities Inspection	Mahesh Ramanadham 11/14/2011 via email
OSI/DGCPC	Kassa Ayalew, Susan Thompson 11/2/2011
OSE/DMEPA Proprietary Name	Walter Fava, Carlos Mena-Grillasca, Carol Holquist 11/4/2011
OBP Review Name, carton/container label	Kimberly Rains, Sarah Kennett, Patrick Swann 8/30/2011
OSE/DMEPA Labeling Review	Walter Fava, Carlos Mena-Grillasca, Carol Holquist 8/5/2011
OPDP/DPP (formerly DDMAC)	Christine Corser 10/13/2011
Pediatric Review Committee	Pediatric studies waived 6/17/2011
Advisors and Consultants Staff	Yvette Waples 6/17/2011

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OC/OMPQ/DGMPA/BMAB=Office of Compliance, Office of Manufacturing Product Quality, Division of Good Manufacturing Practice Assessment, Biotech Manufacturing Assessment Branch; formerly
OC/DMPQ/MAPCB/BMT = Office of Compliance/Division of Manufacturing and Product Quality/Manufacturing and Pre Approval Chemistry Branch/ Biologics Microbiology Team
OPS/OBP/DMA = Office of Pharmaceutical Sciences/Office of Biologics Products/Division of Monoclonal Antibodies
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPP=Office of Prescription Drug Promotion/Division of Professional Promotion; formerly,
DDMAC=Division of Drug Marketing, Advertising and Communication
PMHT=Pediatric and Maternal Health Staff

Table of Contents:

1. Summary and Recommendations

Aflibercept is a human fusion protein that is proposed for the treatment of neovascular (wet) age-related macular degeneration (AMD), given in a regimen of 2 mg (0.05 mL of 40 mg/mL solution) by intravitreous injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg via intravitreal injection once every 8 weeks (2 months). Dosing can be given as frequently as every 4 weeks based on the results of both Phase 3 studies, but no added benefit was seen with more frequent dosing. Injection must be administered by a qualified physician under aseptic conditions including surgical hand disinfection, sterile gloves, drape and eyelid speculum. The product is supplied in a single-use sterile glass vial with a (b) (4) stopper and an aluminum crimp seal.

Based on the review of BLA 125387, the product quality reviewers and the product microbiology sterility reviewers identified multiple deficiencies during the initial 6 month review period that needed to be resolved before the application could be approved. Regeneron provided multiple submissions to address these issues, including a major amendment submitted on August 12, 2011. The FDA accepted this major amendment for review and issued a letter on August 17, 2011 extending the PDUFA goal date from August 18, 2011 to November 18, 2011, to provide time for review of the major amendment. In addition, Regeneron amended the BLA (b) (4) single-use vial to be reviewed for approval during the extended review cycle. Because the list of outstanding deficiencies identified during the first six months of the review cycle was extensive, the Product Quality review staff and Regeneron held biweekly teleconferences from August through October 2011 during which all deficiencies were systematically discussed and Regeneron provided the information and documentation necessary to address each of the deficiencies. In addition to addressing the Product Quality deficiencies, Regeneron agreed to six post-marketing commitments (PMC) from Product Quality and one PMC from Quality Microbiology that are summarized in Section 1.2 and itemized in Section 13.3.

Other disciplines, including clinical, statistical, pharmacology/toxicology, clinical pharmacology, recommended approval of the application.

Review of the package insert, carton and container labeling was undertaken and included comments from each of the review disciplines as well as staff from DMEPA, OPDP/DPP and OBP. The trade name Eylea was found acceptable by DMEPA. The proper name[2] was designated as aflibercept.

The Office of Scientific Investigations recommended that clinical trial data and sponsor inspections are acceptable.

[2] Biologics regulations refer to the name of the active ingredient as the proper name, for small molecules the name of the product is called the established name and includes the active moiety and dosage form.

Compliance recommended that all facilities are acceptable and there are no pending or ongoing compliance actions that prevent approval. The (b) (4) facility was granted a waiver from inspection because it has recently been inspected and found acceptable.

I recommend Regeneron be issued an *Approval* letter for Eylea (aflibercept).

1.1 Deficiencies

None.

1.2 Post-Marketing Studies:

Post Marketing Requirements (PMR)
The Medical Officer recommends 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."

Post Marketing Commitments (PMC)
The company has agreed to seven PMCs, which include (1) to investigate hold times for the (b) (4) vial presentation product quality, (2) to confirm (b) (4) (b) (4) purification from 3 lots, and to re-evaluate release and shelf-life specifications for (3) drug product, (4) drug substance, (5) drug intermediate and (6) formulated bulk after 30 commercial manufacturing runs, and (7) hold time validation studies with three lots of 40 mg/ml aflibercept manufactured at the (b) (4) vial site, including bioburden and endotoxin data from samples taken at the end of the hold times.

1.3 Other Issues

None.

2. Background

Age-related macular degeneration (AMD) is a progressive eye condition affecting as many as 15 million Americans, with 200,000 new cases each year. AMD causes severe vision loss because it affects the macula of the eye, where the sharpest central vision occurs and thereby impacts a person's ability to read, drive, identify faces, watch television, safely navigate stairs and perform other daily tasks. AMD does not cause complete blindness, but leaves only the outermost, peripheral vision and only dim images or holes in central vision. Neovascular or "wet" AMD accounts for about 10% of all AMD cases and is due to formation of abnormal blood vessels behind the retina; these are fragile and may leak blood or fluid. Wet AMD is more severe and causes more vision damage than dry AMD. Dry AMD accounts for 90% of all AMD cases and is due to atrophy and death of cells with thinning of the macula and formation of drusen. [3] [4] The incidence of AMD increases with age, it is more common in women and Caucasians and more common in people with blue eyes because they may sustain more ultraviolet damage from the sun.

[3] http://www.amd.org/
[4] http://nihseniorhealth.gov/agerelatedmaculardegeneration/wetamd/01.html

Currently approved therapies for wet AMD include

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 sodium injection)	December 2004	Indicated for the treatment of neovascular (wet) age-related macular degeneration
BLA 125156	Lucentis (ranibizumab injection)	June 2006	Indicated for the treatment of patients with neovascular (wet) age-related macular degeneration

Source: Dr Wadhwa's review
Pegaptanib (drug) and ranibizumab (biologic) are selective VEGF antagonists, preventing VEGF from binding VEGF-receptors and suppress ocular pathological neovascularization
*Avastin (bevacizumab) is an anti-VEGF monoclonal IgG1 antibody and is approved for treatment of metastatic colorectal cancer, non-small cell lung cancer, glioblastoma, and metastatic renal cell carcinoma. It is used off label to treat AMD; pharmacies repackage the intravenous solution for intravitreal administration.

Regeneron submitted the application for Eylea (aflibercept) on February 17, 2011 and included two Phase 3 trials, each of which tested three regimens of aflibercept and compared each to the approved Lucentis regimen. These clinical trials demonstrated that aflibercept was non-inferior to the approved product Lucentis (ranibizumab injection).

2.1 Priority Review

The applicant requested priority review, because wet AMD is a serious, sight-threatening disease and Eylea was considered to offer a significant improvement to available therapies. One of the regimens evaluated in Phase 3 trials was a 2 mg dose given every 8 weeks (following three loading doses of 2 mg given every 4 weeks). The currently approved Lucentis regimen is labeled for injection every 4 weeks, therefore the benefit that Eylea could be injected once every 8 weeks instead of every 4 weeks led to the decision to grant a Priority Review for this BLA.

2.2 Nomenclature

The applicant stated that VEGF-Trap is a recombinant protein consisting of specific domains of the human VEGF receptors, VEFGR-1 and VEGFR-2 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; it's a decoy receptor for VEGF. The molecule is known as aflibercept. (b) (4) The trade name Eylea was considered acceptable by DMEPA.

2.3 Meetings with company during development, including pre-BLA meetings

IND 12462 was submitted May 16, 2005. Special protocol assessment (SPA) no agreement letters were issued March 5 and July 13, 2007 for VGFT-OD-0605. Since then, the Phase 3 protocols were amended and the 12-month data from these 24-month trials have been submitted to the BLA.

During a meeting on June 1, 2009, the preclinical program was discussed and the scope of the program appeared consistent with available guidance documents and was in general acceptable.

During the September 15, 2009 meeting, FDA and Regeneron discussed specific aspects of manufacturing: (b) (4) There was discussion of stability data for the vial presentation and finally comments about need for complete list of manufacturing sites, manufacturing schedule to plan inspection dates, and extensive guidance on information to include in the application. (b) (4) (b) (4)

A pre BLA meeting was held with the Division of Anti-Infective and Ophthalmology Products on September 8, 2010 to discuss the clinical sections (Module 5) of the BLA, and plans to support the BLA with data from the Phase 2 dose ranging study VGFT-OD-0702 and the two Phase 3 studies VIEW 1 and VIEW 2. The Division stated that the final marketing configuration of the product and container approved should be one(s) that had been evaluated in clinical trials and any variations in the presentation or alternate dispensing devices were not appropriate, namely a labeling statement that the product could be used with "any other suitable needle," is highly unlikely. The Division stated that a sterilized needle should be co-packaged with a sterilized syringe. In addition the Division stated that sterility of ophthalmic preparations and dispensers is required by regulations (21 CFR 200.50). (b) (4)

Product Quality and Quality Microbiology groups met for a pre-BLA meeting on September 27, 2010 and discussed sterility testing, blister integrity of the package components, comparability studies, the vial presentation (b) (4) shelf life, analytical validation/qualification, anti-drug antibody, and information that should be included in the CMC Drug Substance (DS) section and the Drug Product (DP) section of the BLA. In addition there was a listing of the validation data summaries, discussion of facilities, manufacturing schedule, and option of pre-submitting portions of the application.

Comment:
As noted in the regulations, (21 CFR 200.50) an ophthalmic drug along with the device used to dispense the drug are both regulated as drugs for ophthalmic products; therefore each proposed marketing presentation needs to be reviewed individually to assure sterility. The importance of sterilization and other product quality issues was discussed with the company during the pre-BLA meeting as well as during several meetings during drug development.

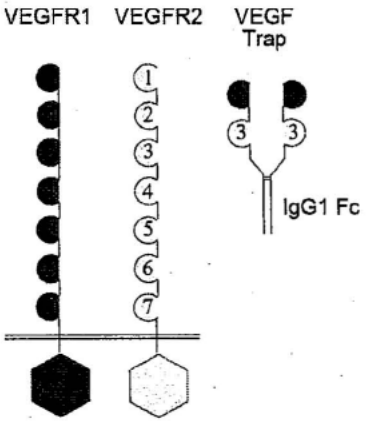
2.4 Aflibercept BLA submission

The BLA was submitted February 17, 2011 and an acknowledgement letter sent March 8, 2011. The filing letter was sent April 15, 2011 (stated PDUFA goal is August 20, 2011) and the application was filed under 21 CFR 601.2(a). The expectation was noted that proposed labeling would be communicated July 23, 2011.

As summarized in Section 3 below, there were multiple requests for additional CMC and sterility data during the review period, and multiple amendments submitted to the application to address CMC and sterility issues. A major amendment was accepted August 12, 2011 and a letter issued August 17, 2011 extended the PDUFA goal date to November 18, 2011.

3. CMC/Product Quality Microbiology

The product quality reviewer notes that aflibercept is a dimeric IgG1 fusion protein consisting of Fc portion of human IgG1 and vascular VEGFR-derived peptide domains. The Fc portion is fused to individual dimers which consist of VEGFR-2 domain 3 fused to VEGFR-1 domain 2. The molecule has (b) (4) molecular weigh of 115kD (including glycosylation).



The drug product (aflibercept) is supplied as a sterile, preservative free liquid formulation of 2 mg/0.05mL (40 mg/mL) aflibercept in sterile, single-use glass vial filled to a target of 0.278 mL and intended to deliver 0.05 mL (50 microliters) of aflibercept (40 mg/mL) aqueous solution.

The solution includes 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% (w/v) polysorbate 20, and 5% sucrose, pH 6.2. It does not contain a preservative so any unused portion of vial contents must be discarded.

The product should be refrigerated at 2°C to 8°C (not frozen) and protected from light.

Dr. Kennett's and Dr. Fuch's reviews provide details on the manufacturing of aflibercept in a Chinese Hamster Ovary K1 cell line using (b) (4)

Dr. Suvarna's review summarizes drug substance sterility evaluation and Dr. Thomas provides a summary of drug product sterility evaluation.

Summary of Submissions

Early in the review of the application it was noted that adequate detail regarding the manufacturing and quality of the product was not available and therefore multiple requests for clarification and other information was requested.

- The updated manufacturing schedule was sent March 10, 2011.
- In response to a series of FDA requests, Regeneron provided the following information. On March 24, 2011 batch records, LOA for DMFs, pyrogen testing of DP and clarification of dosage forms to be commercialized was submitted to Modules 1.11.1, Module 3.2.R and Module 1.4.1.
- On April 4, 2011 qualification data for the bioburden and endotoxin test methods used for testing (b) (4) and data evaluating microbial control over DS manufacturing process, clarification of DS shipping validation studies was submitted. Further information on remaining qualification data (b) (4) was provided April 13, 2011.
- (b) (4)
- On April 11, 2011 information on the rabbit pyrogen test, stating no rabbit developed pre-defined temperature rise demonstrating absence of pyrogens in accordance with USP. Information on the process for (b) (4) sterilization method was submitted. On the same day Regeneron also provided responses to questions regarding vial manufacturing at (b) (4) and requested exemption from 21 CFR 610.12 requirements for bulk sterility.
- (b) (4)
- On April 29, 2011 Regeneron provided 9 months of stability data for Vials manufactured by (b) (4) (b) (4)
- On May 23, 2011, Regeneron provided responses to various questions on manufacturing, process validation, and specifications.
- On June 7, 2011, microbiology information on vials (b) (4) was submitted.
- On June 20 and June 28, 2011 Regeneron submitted qualification reports for extended characterization assays.
- On June 30, July 5, and July 8, 2011, Regeneron submitted information on 25 questions related to DS manufacturing; this information could not be reviewed in the current 6-month cycle and allow reviewers to meet the 21st century review timelines.
- The original application included (b) (4) (b) (4) (b) (4) 40 mg/mL (b) (4) However, based on recommendations from the Advisory Committee and Division that the 2 mg dose (40 mg/mL formulation) given every 8 weeks was effective and provided patients with the advantage of less frequent intravitreal injections, Regeneron decided to send an amendment (b) (4) (b) (4) from the BLA on August 1, 2011.
- Reviews were completed and a list of 43 deficiencies (including 24 previously communicated via IR letters) was included in the final reviews and communicated to

Regeneron August 3, 2011. (b) (4) [redacted]

- The company sent in amendments on August 5, 2011 and August 12, 2011. The latter submission was classified as a major amendment, extending the PDUFA goal date by 3 months to November 18, 2011.
- Subsequently, Product Quality reviewers and Regeneron held biweekly teleconferences to address the extensive outstanding deficiencies within the following topics.
  - Data supporting release methods and acceptance criteria for Drug Substance and Drug Substance Intermediate.
  - Data supporting stability of Drug Substance and Drug Substance Intermediate.
  - Drug substance (DS) and drug Substance intermediate (DSI) manufacturing process, process controls and process validation.
  - Data supporting release methods and acceptance criteria for Formulated Bulk Drug Product and Drug Product.
  - Data supporting stability of Formulated Bulk Drug Product and Drug Product
  - Formulated Bulk Drug Product (FB) and Drug Product (DP) manufacturing process controls and process validation.
  - Immunogenicity assay validation
- The dates of the teleconferences and documentation are provided below:

Communication/Documents	Date
Information Request	8-3-2011
Teleconference	8-4-2011
Teleconference	8-10-2011
Pre-meeting Document	9-2-2011
Sponsor Meeting	9-2-2011
Pre-meeting Document	9-9-2011
Teleconference	9-13-2011
Pre-meeting Document	9-26-2011
Teleconference	9-27-2011
Pre-meeting Document	10-6-2011
Teleconference	10-6-2011
Pre-meeting Document	10-17-2011
Teleconference	10-18-2011
Pre-meeting Document	10-21-2011
Teleconference	10-25-2011
PMC Agreements	11-8-2011
Information Requests	11-9-2011

- Amendments submitted to address the deficiencies and reviewed during the last three months of the extended review cycle were submitted to the BLA on the following dates.

Submissions	Document Date
125387/0.23	7-1-2011
125387/0.24	7-6-2011
125387/0.25	7-8-2011
125387/0.27	7-19-2011
125387/0.28	7-21-2011

125387/0.29	8-1-2011
125387/0.30	8-5-2011
125387/0.31	8-10-2011
125387/0.32	8-12-2011
125387/0.33	9-1-2011
125387/0.34	9-1-2011
125387/0.36	9-12-2011
125387/0.37	9-20-2011
125387/0.38	9-27-2011
125387/0.39	10-7-2011
125387/0.40	10-21-2011
125387/0.42	10-27-2011
125387/0.44	11-9-2011

Review Conclusions:
Based on their final review, Dr Kennett and Dr Fuchs conclude that:

> The data submitted in this application are adequate to support the conclusion that the manufacture of Eylea (aflibercept) is well controlled, and will lead to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated and a consistent product was produced form the multiple production runs presented. We recommend that this product be approved for human use (under conditions specified in the package insert).

[redacted] (b) (4)

The product quality microbiology reviewer, Dr. Suvarna found the drug substance information adequate, and Dr. Thomas found that with the [redacted] (b) (4) and resolution of the deficiencies with the [redacted] (b) (4) vial, the application could be approved. She requested one PMC to evaluate bioburden and endotoxin following a hold validation study.

The description of the 40 mg/mL glass vial from [redacted] (b) (4) is provided below:

NDC NUMBER	CARTON TYPE	How Supplied: CARTON CONTENTS
61755-005-02	Vial	one single-use, sterile, 3-mL, glass vial containing a 0.278 mL fill of 40 mg/mL aflibercept injection one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert

Source: Package insert

Regeneron requested and was granted claim of categorical exclusion for environmental assessment under 21 CFR 25.15(b), based on the estimated concentration of the substance at the point of entry into the aquatic environment being below 1 ppb.

Comments:
As stated above, the Product Quality and Microbiology Sterility reviewers recommend approval of the (b) (4) *single-use vial product. Regeneron has agreed to six post-marketing commitments (PMC) for Product Quality and one PMC from Microbiology.*

The above amendments included information that was designated as "new," as well as information that served to "replace" some BLA sections. In retrospect, the complexity of the application, the need for multiple submissions and clarifications despite pre-BLA meetings to discuss CMC on September 15, 2009 and September 27, 2010, indicate that although technically the application was filed because "on the surface" the application included the proposed presentations and information on manufacturing and controls, in fact the information was insufficient to establish the purity, potency and stability of the aflibercept products. The use of the term new to designate information submitted to the BLA suggests that the application, in retrospect, was not a complete application at the time of the original submission.

4. Nonclinical Pharmacology/Toxicology

The results of studies are summarized in the Pharmacology/Toxicology review by Dr. Maria Rivera. Multiple pharmacology and toxicity studies were reviewed; including studies in which aflibercept was administered IV, subcutaneously and intravitreal (IVT) in various species. She notes that the monkey was the most relevant species to test the toxicity of aflibercept in the eye. Following IVT administration of aflibercept, the eyes showed mild anterior segment and vitreous inflammation judged to be clinically insignificant.

Unexpectedly, epithelial erosion and ulceration of nasal turbinates was seen after IVT administration. This finding had not been seen with previous anti-VEGF products. Patients were monitored for this adverse effect in clinical trials and no similar pathology was seen. The animal finding will be summarized in the labelling:

> **13.2 Animal Toxicology and/or Pharmacology**
> Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg/eye. At the NOAEL of 0.5 mg/eye in monkeys, the systemic exposure was 42 times and 56 times higher based on C_{max} and AUC, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg.
> Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

Following IV administration in monkeys, target organs included bone, kidney, adrenals, ovary and nasal cavities, with vascular changes noted in the brain and GI tract. Animal exposures after IV administration were well in excess of the exposure in humans with IVT administration. (See table below from Dr. Rivera's review.)

Table: Safety Margins for Systemic Toxicities Based on the Animal and Human Free VEGF Exposures

Study Type / Study No.	Free VEGF Trap in Plasma			Exposure Ratios[a]	
	Dose	C_{max}[b] (µg/mL)	AUC_{0-t} (µg•h/mL)	Based on C_{max}	Based on AUC
Phase I VEGF Trap-Eye Pharmacokinetic Sub-study in Humans Module 5.3.3.2, VGFT-OD-0702.PK	2 mg/eye	0.0193	2.856	NA	NA
Cynomolgus Monkeys					
13-Week IVT Toxicity Module 4.2.3.2, VFGT-TX-04025	NOAEL: ND				
	LOAEL: 1 mg/eye[c]	2.45	384	127	135
8-Month IVT Toxicity Module 4.2.3.2, VFGT-TX-05011	NOAEL: 0.5 mg/eye[d]	0.802	160	42	56
	LOAEL: 2 mg/eye[e]	4.46	2023	231	708
6-month IV Toxicity Module 4.2.3.2, VFGT-TX-05009	NOAEL: ND				
	LOAEL 3 mg/kg[f]	94.6	4416	4902	1546
3-month IV Toxicity in Juveniles Module 4.2.3.2, VFGT-TX-05010	NOAEL: ND				
	LOAEL: 0.5 mg/kg[g]	9.71	384	503	134
Rabbits					
Reproductive IV Toxicity Module 4.2.3.5.2, VFGT-TX-06002					
Maternal toxicity	NOAEL: 3 mg/kg[h]	56.1	1935	2907	678
Embryo-Fetal toxicity	NOAEL: ND				
	LOAEL: 3 mg/kg	56.1	1935	2907	678

AUC = Area under the concentration time curve; C_{max} = Maximal concentration; GD = Gestation day; IV = Intravenous; IVT = Intravitreal; NA = Not applicable; ND = Not determined; NOAEL = No observed adverse effect level; LOAEL = Lowest observable adverse effect level; T_{max} = Time of maximal concentration, VEGF = Vascular endothelial growth factor.

[a] –

Changes to female and male reproductive organs were seen including alterations in hormone levels, compromised luteal development, reduction in maturing follicles, absent menses, changes in sperm morphology and sperm motility; these types of changes had been seen with other anti VEGF products. Based on C_{max} and AUC for free aflibercept observed at the lowest dose used (3 mg/kg), the systemic exposures were approximately 4900 times and 1500 times higher, respectively, than seen after the 2 mg intravitreal dose.

Primary pharmacology studies showed VEGF-Trap reduced choroidal neovascular (CNV) lesions in monkeys, reduced leakage from retinal vessels in the diabetic rat model and blocked abnormal vessel formation in the mouse hyperoxia model, compared to control animals.

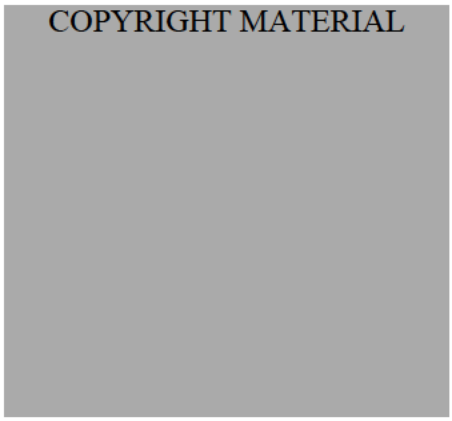
VEGF is involved in organogenesis, and aflibercept was embryotoxic and teratogenic with dose related increased in fetal malformations and fetal loss in rabbits. At 3 mg/kg, the systemic exposures based on C_{max} and AUC for free aflibercept were approximately 2900- and 600-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg. Pregnancy Category C is recommended.

Systemic rat and mouse studies showed elevation in blood pressure, another class effect. Such elevations were not seen after IVT administration. During the June 1, 2009 meeting, the division agreed that carcinogenicity studies were not required. The applicant noted that the complement assay used in the 8-month IVT monkey toxicology study was not validated but this did not impact interpretation of results.

Comment:
The application is recommended for approval from a pharmacology/toxicology standpoint and labeling revisions have been finalized.

5. Clinical Pharmacology/Biopharmaceutics

As summarized in Dr. Zhang's clinical pharmacology review and in proposed labeling, aflibercept is a fully human, water-soluble recombinant decoy VEGF receptor, biologically engineered to contain the key extracellular VEGF-binding domains of the VEGF receptor-1 (domain 2) and VEGF receptor-2 (domain 3) fused to the constant Fc region of IgG1. Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF-A binds to VEGFR-1 and VEGFR-2, two receptor tyrosine kinases present on the surface of endothelial cells. PlGF binds only to VEGFR-1, present also on the surface of leucocytes.



The above Figure is from:

http://upload.wikimedia.org/wikipedia/commons/c/c8/VEGF_receptors.png

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

EYLEA is administered intravitreally to exert local effects in the eye. In patients with neovascular (wet) AMD, following intravitreal administration aflibercept, 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 to patients with wet AMD, the mean C_{max} of free aflibercept in the plasma 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 intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

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 intravenous administration of doses of 2 to 4 mg/kg aflibercept. No dose adjustment based on renal impairment status is needed.

Comment:
The reviewer recommends approval from the clinical pharmacology perspective; no phase 4 studies are requested.

6. Clinical Microbiology/Immunology

Primary pharmacology studies in animals are included in Dr. Rivera's review and summarized in Section 4.

7. Clinical/Statistical-Efficacy

As summarized in Dr. Wadhwa's review, aflibercept was evaluated in a comprehensive clinical program that included two Phase 1 studies examining intravitreal doses of 0.5 mg to 4 mg (VGFT-OD-0502 and VGFT-OD-0603); one dose-ranging Phase 2 study (VGFT-OD-0508) examining 0.5 mg, 2 mg every 4 weeks and 0.5 mg, 2 mg and 4 mg every 12 weeks and an open-label long term safety study VGFT-OD-0702 which enrolled subjects previously enrolled in VGFT-OD-0502, -0508, and -0603. These patients continued to be treated with aflibercept and 99 received aflibercept from the pre-filled syringe (PFS) presentation.

Two Phase 3 clinical trials (VGFT-OD-0605/14393 called **VIEW 1** and VGFT-OD-0618/311523 called **VIEW 2**) were also conducted. VIEW is an acronym for **V**EGF-Trap-Eye **I**nvestigation of **E**fficacy and Safety in **W**et AMD.

7.1 Phase 3 clinical trials

The primary objective of the two trials was to assess the efficacy of intravitreally administered aflibercept compared to ranibizumab in a non-inferiority trial in preventing moderate vision loss in subjects with all sub-types of neovascular AMD. Patients were randomized 1:1:1:1 to one of four regimens in this double-masked trial.

- 2 mg aflibercept administered every 4 weeks (2Q4)
- 0.5 mg aflibercept administered every 4 weeks (0.5Q4)
- 2 mg aflibercept 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 given every 4 weeks
- 0.5 mg ranibizumab administered every 4 weeks (RQ4)

The choice of the treatment arms is summarized by Dr. Zhuang in the Statistical review and is based on outcomes in the Phase 2 trial, VGFT-OD-0508:

> The choice of the final dose groups in the Phase-3 program, i.e., 0.5Q4, 2Q4, and 2Q8, was based on the results of Study VGFT-OD-0508. Over the first 12 weeks, 100% of patients in the 2Q4 treatment group and 0.5Q4 treatment group maintained vision (defined as losing less than 15 letters on the ETDRS scale). In addition, the improvements in visual acuity were similar in the two 2 mg groups at Week 8, suggesting that an 8-week dosing interval could potentially maintain the effects of VEGF Trap-Eye in Phase-3 studies. The time course of improvements also suggested that initiating treatment with three monthly injections was associated with a better outcome than a single injection of either 2 mg or 0.5 mg. In the PRN phase, a greater percentage of patients in the 2-mg group maintained vision than in the 0.5-mg group, indicating that efficacy of the 0.5-mg dose is more sensitive to dosing interval than efficacy with the 2-mg dose. Dosing with 4 mg did not result in greater efficacy than dosing with 2 mg.

The Phase 3 trials were designed to follow patients for 96 weeks; per agreement with FDA, 52 week data were submitted to support approval.[5] Details of the trial including inclusion and exclusion criteria and study procedures can be found in the clinical reviews by Drs. Wadhwa, Boyd and Chambers.

The patients enrolled in these trials were >50 years of age, had subfoveal CNV, best corrected visual acuity (BCVA) 20/40 to 20/320 (letter score 73 to 25).[6] During the first 52 weeks of the trial, dosing was administered based on a fixed schedule, during the second 52 weeks dosing could be given between every 4 weeks to every 12 weeks based on patient's individual response. Sham injections were given in the first 52 weeks to preserve masking, sham injections were not given in the second 52 weeks (year).

Demographics

In VIEW 1, the population had a mean age of 78 years (range 49-99 years), 59% were female, 97% were white, 34% had dark eye color. At baseline, the mean visual acuity letter score was 55 (range 10-85). The retinal thickness was 266 micrometers, the area of CNV was 6.6 mm^2

[5] While the number of weeks correspond to approximately 2 years (96 weeks) and 1 year (52 weeks), in this review the number of weeks is reported instead of rounding information to months or years because such rounding has previously led to confusion with scheduling and reimbursement (OAP/DTOP internal discussion).
[6] This range covers mild vision loss to severe vision loss: http://www.precision-vision.com/index.cfm/feature/9/a--visual-acuity.cfm

and the total lesion was 7 mm^2. The lesions were 38% occult, 34% minimally classic and 27% predominantly classic. The mean NEI VFQ-25 score was 71.[7]

In VIEW 2, mean age was 74 years (50 to 93 years), 56% were female, 73% were white, 21% Asian, 60% had dark eye color. At baseline the mean visual acuity letter score was 52. The retinal thickness was 332 micrometers, the area of CNV 7.8 mm^2, and the total lesion 8.2 mm^2. The lesions were 38% occult, 35% minimally classic and 26% predominantly classic. The mean NEI VFQ-25 score was 72.

Comment:
The demographic characteristics were reasonably balanced across the arms, and similar to study populations in previous studies. Patients in VIEW 2 had greater retinal thickness and somewhat larger lesions than patients in VIEW 1.

Per Dr Zhang, the clinical pharmacology reviewer, pharmacodynamic (PD) evaluation included assessment of optical coherence tomography (OCT) to measure retinal and subretinal fluid accumulation and thickness of AMD lesions. Fluorescent angiography (FA) was done to provide morphological insight to the PD effects at the target site. These variables were considered surrogates; the efficacy endpoints are defined below.

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[8] letter score compared to baseline.

Per Dr Zhuang, statistical analyses were pre-specified (see review for complete details). The analysis of the primary endpoint used a step-wise conditional sequence of 2Q4, 0.5Q4 and 2Q8 compared to RQ4 and the 95.1% CI was used to account for the alpha adjustment of 0.1% as a result of IDMC safety assessments. (p 27). Once NI was established, the data were examined for superiority; however, no superiority of aflibercept compared to ranibizumab was shown.

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

Treatment failure during the first 52 weeks of the study was defined as a decrease from baseline in best corrected visual acuity (BCVA) by 15 or more letters (3 lines on ETDRS) at

[7] NEI VFQ-25 = National Eye Institute Visual Function Questionnaire consists of 25 questions that cover the scope of general health and vision, ocular symptoms, color vision and peripheral vision, impact on activities and function, and measures of social functioning, driving, and level of dependence.
[8] ETDRS or Early Treatment Diabetic Retinopathy Study eye chart has become standard in evaluating vision and were developed and used by the National Eye Institute which conducted the ETDRS study to evaluate laser versus aspirin treatment in patients with diabetic retinopathy. This chart has the same number of letters in each line (five), thus a gain in one line is analogous to a gain of 5 letters. A familiar chart used in many offices is the Snellen chart, available since the late 1800's had a different number of letters per line, ranging from 1 to 10 and different spacing.

2 consecutive assessments, 4 weeks apart. A subject who was considered a treatment failure could be, but was not required to be, discontinued from treatment and was evaluated at the 96 week visit.

7.2 Efficacy Results

Per Dr. Zhuang, in VIEW 1, a total of 1217 patients were randomized at 154 sites in the US and Canada, 1215 were included in the safety and 1210 in the efficacy full analysis set (FAS). In VIEW 2, a total of 1240 patients were randomized in 186 centers in 26 countries in Europe, South America, Australia, and Asia, 1204 were included in the safety and 1202 in the efficacy FAS.

Primary Endpoint

The efficacy for each of the Phase 3 clinical trials is summarized in the following tables:

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)

Adapted from Dr. Wadhwa's review

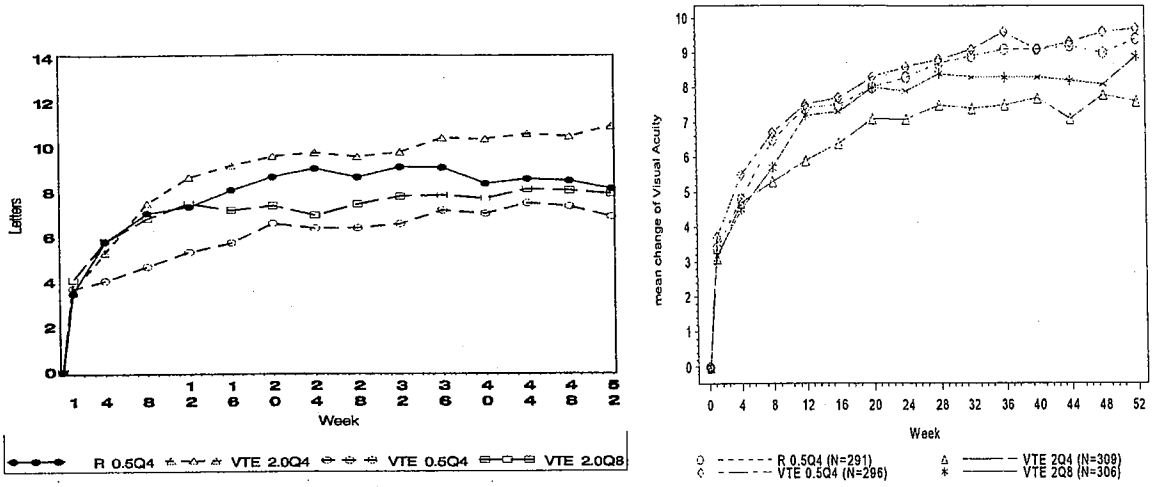
VIEW #2: Primary Efficacy Analysis (FAS Population with LOCF)

	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 (-5, 2.6)	-2.3 (-5.9, 1.4)	-1.6 (-5.3, 2.2)

Mean change from baseline through week 52 in ETDRS Letter Score (LOCF) full analysis set (VIEW1 and VIEW 2)



All three doses of aflibercept were judged non-inferior to ranibizumab for BCVA, and in all analyses the results would have met a margin of 5% (although a 10% margin was chosen). None of the secondary analyses showed any significant difference between the aflibercept arms and ranibizumab.

In Study VIEW #2, the applicant did not adjust the CI to 95.1% for the interim safety look. The statistical reviewer requested sensitivity analyses from Regeneron (submitted on May 11, 2011). These analyses used multiple imputations approaches for handling missing data, and adjusted the CI as appropriate. The reviewer concluded that aflibercept was non-inferior to ranibizumab in VIEW #2 also.

Various demographic subgroup analyses showed results to be consistent with the total population.

Secondary endpoints

- Change in week 52 letter score: The letter score at baseline was a mean of around 55, and rose to low to mid 60's by 52 weeks. In VIEW 1, the change was significantly better for the 2Q4 regimen compared to control, but this findings was not reproduced in VIEW 2. For all other arms, there were no significant differences between aflibercept and ranibizumab.
- BCVA at 52 weeks: The BCVA score was significantly higher between the 2Q4 regimen and control in VIEW 1, but was not corroborated in VIEW 2 and for all other arms, there were no significant differences between aflibercept and ranibizumab.
- The proportion of patients who gained more than 15 letters was also higher in VIEW 1 2Q4 arm, although it did not reach statistical significance. There were no differences among other arms. Approximately 1/3 of patients gained 15 letters on ETDRS visual acuity.

Comment:
Although there was a significant letter score gain and improvement in BCVA in the 2Q4 arm, these results were not reproduced in the second trial and were not seen in the proposed

treatment regimen of 2Q8 regimen. The outcome in the secondary analyses supports the findings of non-inferiority for the primary endpoint.

7.3 Noninferiority Margin:

The control in the VIEW 1 and VIEW 2 studies is ranibizumab 0.5 mg given every 4 weeks (every month). Data on the efficacy of this control product is presented in the Lucentis (ranibizumab injection) package insert,[9] and the results of the controlled clinical trials have also been published. In these studies, efficacy was measured as the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared to baseline. Patients with classic, minimally classic and occult AMD were enrolled in these trials.[10]

In study AMD-1 (published as MARINA in 2006)[11] visual acuity was 95% for ranibizumab 0.5 mg and 62% for sham treatment (each given every 4 weeks), which is a difference of 32% and 95% CI (26%, 39%).

In a second study AMD-2 (published as ANCHOR in 2006)[12] the efficacy rates using the same time and endpoint were 96% ranibizumab and 64% verteporfin, with a 33% difference and 95% CI (25%, 41%).

In a third study AMD-3 (published as PIER in 2008)[13] visual acuity improved with monthly dosing but returned to baseline when dosing was reduced to every 3 month. The publication reported visual acuity rates of 90% for ranibizumab and 49% for sham control, a difference of 41%.

Therefore, a 10% NI margin conserves over half of the treatment effect, using the most conservative estimate of the treatment effect from these trials.

Comment:
The clinical and statistical reviewers concluded that both of the 2 mg dose regimens of aflibercept are non-inferior to ranibizumab and effective in the treatment of AMD. They recommend approval. The Medical Officer recommends that a PMR to collect data on endothelial cell count be requested, as has been done with previous products, to assess the safety of repeated aflibercept intravitreal injections.

8. Safety

The safety evaluation is summarized in the reviews by Dr. Wadhwa, Dr. Boyd, and Dr. Chambers. Safety data were available for 1824 patients on aflibercept from the two phase 3

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[9] Lucentis package insert http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125156s053lbl.pdf
[10] Classic AMD is defined as well defined lesions of new blood growth detected on clinical exam with fluoresceint angiography and considered related to more severe and rapid vision loss than occult AMD. Minimally classic AMD is the term applied when the classic component is less than 50% of the total lesions. Occult AMD is the presence of ill defined lesions on fluorescein angiography, or the absence of classic AMD. http://www.webrn-maculardegeneration.com/classic-AMD.html
[11] Rosenfeld PJ et al for the MARINA Study Group, *NEJM* 2006; 355(14):1419-1431.
[12] Brown DM et al for the ANCHOR Study Group, *NEJM* 2006; 355(14):1432-1444.
[13] Regillo CD et al for the PIER Study Group, *Am J Ophthal* 2008; 145:239-248.

studies, (safety analysis set, stats review). In clinical trials approximately 89% (1616/1817) were 65 years of age or older, 63% were 75 years of age or older. There were no differences in outcome based on age.

Approximately 90% of patients completed these 2 trials, a small number of patients died (events do not appear drug related) or discontinued the trials for various reasons. Serious ocular adverse reactions were infrequent; endophthalmitis was reported in 8 patients.

Aflibercept is contraindicated in patients with hypersensitivity, with ocular and periocular infections, and with active intraocular inflammation.

8.1 Adverse Reactions of Special Interest

Nasomucosal examination

Anti VEGF products have been associated with findings of nasomucosal erosion in animal studies; therefore a special ENT examination was done on a subset of patients (approximately 160 patients, 40 per dose). The findings from these exams included occasional nasal septal deviation, rhinorrhea, epistasix, nasal polyps, turbinate hypertrophy, nasal dryness, and cysts. Erosions found in animal studies were not reported in patients.

Endophthalmitis and Retinal Detachment

Eight patients developed endophthalmitis, detachment of retinal pigment epithelium was noted in 3% and retinal pigment epithelium tear in 2% of patients. These events can also be seen as complications of intravitreal injection.

Arterial Thromboembolic Events (ATE)

The incidence of ATE in the VIEW1 and VIEW2 wet AMD clinical trials during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.7% (10 out of 595) in patients treated with ranibizumab. These events included non-fatal MI, non-fatal stroke or vascular deaths reported, with no significant differences between the arms.

Increased intraocular pressure (IOP)

Increased IOP was noted within 60 minutes of intravitreal injection and resolved in most patients before the next pre-dose measurement. Approximately 1% to 4% of patients had IOP measurements of 35 mmHg or greater, or at least a 10 mmHg increase over baseline, most resolved.

Immunogenicity

Serum antibodies to aflibercept were seen in approximately 1% to 5% of patients, and were also seen in the ranibizumab patients who had not received aflibercept, some were judged to be non-drug induced, some were transient, and a few were persistent. The numbers are too small to allow for evaluation of any impact on efficacy.

8.2 Common Adverse Reactions

Aflibercept was evaluated in 1824 patients with wet AMD in the two Phase 3 trials (VIEW 1 and VIEW 2). There were 1223 patients treated with the 2-mg dose (including 610 patients treated with 2 mg q8 week) for 52 weeks, the others received the 0.5 mg dose. Overall the most frequent ocular adverse reactions seen in 5% or more of patients were conjunctival

hemorrhage, eye pain, cataract, vitreous floaters, vitreous detachment and increased intra-ocular pressure; there was no appreciable differences noted between the aflibercept and ranibizumab treatment arms.

Most Common Adverse Reactions (≥1%) in Phase 3 wet AMD studies

Adverse Reactions	**aflibecept (N=1824)**	**ranibizumab (N=595)**
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Conjunctival hyperemia	4%	8%
Corneal erosion	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

9. Advisory Committee Meeting

The application was discussed before the Dermatologic and Ophthalmologic Advisory Committee on June 17, 2011. Based on the Quick Notes by Yvette Waples of the Advisors and Consultants Staff, the committee voted unanimously (10 vs. 0) that the product demonstrated efficacy and safety in neovascular AMD, and recommended the 2 mg every 8 weeks regimen (after 3 loading doses given every 4 weeks). There was discussion that information on injections every 4 weeks could be included in labeling to allow flexibility for scheduling return appointments. Other comments included evaluating the lowest effective dose, including information on increased IOP in labeling, commenting on how to switch patients from other anti-VEGF products to aflibercept.

10. Pediatrics

Age-related macular degeneration only occurs in adult patients, therefore the application was granted a waiver for pediatric studies following the discussion presented before the Pediatric Review Committee on June 1, 2011 and the completed pediatric page emailed to the Division on June 17, 2011 by George Greeley.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection – OBP and OC

Per Dr. Kennett's review (page 6), a pre-approval inspection (PAI) for aflibercept drug substance production at the (b) (4) facility was conducted from (b) (4) (b) (4) by BMAB reviewers Kalavati Suvarna and Lakshmi Narasimhan and product reviewer Sarah Kennett. (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. The final report received from Mahesh Ramanadham via email on November 14, 2011 stated that all facilities were acceptable. (b) (4) manufactures the drug product from formulated bulk from (b) (4) and performs sterility testing for release and stability samples. Inspection of this facility was waived because (b) (4) is a contract manufacturer that produces multiple products using (b) (4), was inspected in March 2010 and no serious deficiencies or systemic problems identified. [Waiver documentation is attached to Dr. Thomas's review of October 13, 2011.]

11.2 Office of Scientific Investigation (OSI) Audits

Inspection of two investigators from VIEW 1 and one investigator from VGFT-OD-702 showed some regulatory violations/deviation resulting in a preliminary classification of VAI while the third investigator was classified as NAI. The final OSI review dated November 2, 2011 concluded that study data were acceptable to support the application and the final classification of the Regeneron inspection conducted (b) (4) was NAI.

11.3 Debarment Certification

Regeneron certified that they had not used services of any debarred individual [as required under FD&C Act Section 306]. One debarred investigator who was initially identified to participate in the study did not enroll any patients before the site was closed.

11.4 Financial Disclosure

Disclosure was provided and several investigators in VIEW 1 and VIEW 2 reported financial arrangements of >$25,000. Dr. Chambers notes that 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.

11.5 Other Regulatory Issues

None identified.

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA, OPDP/DPP and OBP.

- **Package insert (PI):** The PI is written in PLR format and has been reviewed by several of the disciplines, and includes the recommendations made by these groups.

- **Carton and Container Labels**: The labels have been reviewed by OBP and DMEPA.

- **Proprietary Name**: The proposed proprietary name Eylea was reviewed and found acceptable by DMEPA on May 25, 2011 and a letter stating that the name is acceptable was issued by Dr. Holquist of DMEPA on May 25, 2011. The name was re-evaluated and found acceptable on November 4, 2011.

- **Proper Name**: The OBP labeling reviewer recommended that the proper name for this biologic is aflibercept, (b) (4) due to the long-standing practice of naming biologic products based on the drug substance and not including the dosage form. The one exception to this naming convention is Lucentis (ranibizumab injection) which was approved June 30, 2006 for the treatment of AMD. (b) (4) In him Memorandum to the Office Director of OAP, the Deputy Director of DTOP summarized his disagreement with the aflibercept proper name, citing that ophthalmologic products include the dosage form as part of the established name, and Lucentis, a biologic product for AMB, included the dosage form in the established name.[15] Following several teleconferences with the company and internal discussions where potential safety or market delay issues were resolved, and considering that other biologic products referenced by OBP as well as others regulated in the division do not include the dosage form as part of the established name, [16] I concur with the recommendations in the OBP Memorandum.

[14] The discussion of the proper name determination is summarized in the Memorandum dated November 17, 2011 from Kimberly Raines, Pharm D, Labeling Reviewer, Office of Biotechnology Products, to Renata Albrecht, MD, Director, Division of Transplant and Ophthalmology Products (DTOP).
[15] November 16, 2011 Memorandum from Wiley Chambers, MD, Deputy Director, DTOP to Edward Cox, MD, MPH, Director, Office of Antimicrobial Products.
[16] Nulojix (belatacept), Simulect (basiliximab), Zenapax (daclizumab)

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The BLA is recommended for *Approval*, given that all deficiencies have been addressed.

For this biologic product, the following information needs to be included in the approval letter:

> We have approved your BLA for aflibercept effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, aflibercept under your existing Department of Health and Human Services U.S. License No. 1760. Aflibercept injection is indicated for treatment of neovascular (wet) age-related macular degeneration.
>
> Under this license, you are approved to manufacture aflibercept drug substance intermediate, drug substance, and formulated bulk at (b) (4). The final formulated drug product will be manufactured at (b) (4). The final formulated drug product will be labeled and packaged at (b) (4). You may label your product with the proprietary name Eylea and will market it in a (b) (4) vial single-use vial containing 0.278 mL of 40 mg/mL aflibercept, as part of a final packaged product containing the aflibercept single-use vial, a 19-gauge x 1½-inch 5-micron filter needle, a 30-gauge x ½-inch needle and a 1-mL plastic syringe.
>
> The dating period for aflibercept injection shall be 15 months from the date of manufacture when stored at 2 - 8°C. The date of manufacture shall be defined as the (b) (4). The expiration date for the packaged product, (aflibercept injection single-use vials, syringe, needle and filter needle) shall be dependent on the shortest expiration date of any component. (b) (4)
>
> Results of ongoing stability should be submitted to the annual report.
>
> You are not currently required to submit samples of future lots of aflibercept to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.
>
> Any changes in the manufacturing, testing, packaging, or labeling of aflibercept, or in the manufacturing facilities, will require the submission of information to your

biologics license application for our review and written approval, consistent with 21 CFR 601.12.

13.2 Risk Benefit Assessment

Two Phase 3 studies demonstrated that Eylea is safe and effective in the treatment of neovascular (wet) age-related macular degeneration (AMD) at 3 different regimens compared to the approved Lucentis (ranibizumab injection) regimen. The trials were designed as non-inferiority trials; a 10% NI margin was justified based on clinical trials comparing ranibizumab to placebo or photodynamic therapy/verteporfin. All aflibercept doses tested were shown to be non-inferior to the approved ranibizumab regimen (control).

The safety profile of the three aflibercept regimens was acceptable, transient increased intraocular pressure was noted following the intravitreal injection of 0.05mL of Eylea. The labeling will reflect findings of nasal ulcerations seen in monkey studies, and adverse reactions reported during clinical trials: arterial thrombotic events, increased intraocular pressure, immunogenicity, and rare complications of intravitreal injections such as endophthalmitis and retinal detachment. 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.

The new benefit offered by Eylea is that the product was found to be effective when used at a dose of 2 mg (50 microliters of 40 mg/mL solution) every 8 weeks. The approved dosing regimen of Lucentis is intravitreal injection every 4 weeks and off-label use of Avastin is also given every 4 weeks. Less frequent intravitreal injections of a safe and effective drug provide a benefit to the AMD population.

13.3 Recommendation for other Postmarketing Requirements and Commitments

The following PMRs and PMCs will be included in the *Approval* letter:

a) Post-Marketing Requirement

1. Provide clinical information from a 1-year (minimum) clinical trial evaluating the adverse effects, if any, on the corneal endothelium following the intravitreal administration of aflibercept.

   The timetable you submitted on October 24, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2012
Trial Completion:	November 2015
Final Report Submission:	May 2016

b) Post-Marketing Commitments

2. To conduct three drug product hold time studies of the 40 mg/mL vial presentation filled at [redacted] (b) (4) site. Material will be held at commercial scale, and microbiological samples (total viable count, bacterial endotoxin) will be taken at the

end of the hold times. The completed validation report will be submitted as a CBE-0 supplement.

The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: November 2012

3. To conduct three drug product hold time studies for the 40 mg/mL vial presentation filled at the [redacted] (b) (4) site. These studies will include t=0 and end of hold samples for product quality (pH, purity by size exclusion, purity by nrSDS-PAGE, charge variant distribution by IEF, isoaspartate, and potency of aflibercept) evaluation. The completed validation report will be provided as a CBE-0 supplement.

   The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: June 2012

4. To confirm [redacted] (b) (4) by the aflibercept [redacted] (b) (4) process. The clearance study will be performed under protocol on three lots of drug substance produced at the commercial scale. [redacted] (b) (4) will be measured with a validated analytical test method for determining [redacted] (b) (4). The completed method validation and final reports will be submitted in the 2012 annual report by January 2013.

   The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: January 2013

5. To re-evaluate the release and shelf-life specifications for aflibercept drug product after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS within 60 days after completion of the 30th lot manufactured using the commercial process or by December, 2014, whichever occurs first.

   The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: December 2014

6. To re-evaluate the release and shelf-life specifications for aflibercept drug substance after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30

commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS by within 60 days after completion of the 30th lot manufactured using the commercial process or by June, 2013, whichever occurs first.

The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2013

7. To re-evaluate the release and shelf-life specifications for aflibercept drug substance intermediate after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS within 60 days after completion of the 30th lot manufactured using the commercial process or by June, 2014, whichever occurs first.

   The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: June 2014

8. To re-evaluate the release and shelf-life specifications for aflibercept formulated bulk after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS within 60 days after completion of the 30th lot manufactured using the commercial process or by June, 2013, whichever occurs first.

   The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: June 2013

11/18/11
Renata Albrecht, MD
Director, Division of Transplant and Ophthalmology Products

11/18/11
Edward Cox, MD, MPH
Director, Office of Antimicrobial Products