

**Division of Transplant and
Ophthalmology Products
Advisory Committee Meeting
Aflibercept injection**

Sonal D. Wadhwa, MD
U.S. Food and Drug Administration
Medical Officer
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Applicant Information

- Applicant: Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Introduction and Background

- VEGF Trap-Eye (aflibercept) is a recombinant protein.
- VEGF Trap-Eye is a specific antagonist that binds and inactivates circulating VEGF and PlGF.

Drug Information

- Proposed Proprietary Name: Eylea
- Established name: aflibercept injection
- Pharmacologic Category: VEGF inhibitor
- Dosage Form and Route of Administration: intravitreal injection

Applicant Proposed Indication

- Treatment of patients with neovascular (wet) age-related macular degeneration (AMD)

Currently Available Treatments for Proposed Indication

Drug	Approval
Photodynamic therapy (PDT)/Verteporfin	April 2000
Macugen (pegaptanib injection)	December 2004
Lucentis (ranibizumab injection)	June 2006

Introduction and Background

- In comparison:
 - Pegaptanib (Macugen) is an inhibitor of the VEGF165 isomer.
 - Ranibizumab (Lucentis) is an inhibitor of all VEGF-A isomers.

Table of Clinical Trials

Study	Title	Type of Study	Number of Patients
VIEW #1 (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	Safety and Efficacy	1217
VIEW #2 (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	Safety and Efficacy	1240

Primary Objective of VIEW #1 and VIEW #2

- To assess the efficacy of intravitreally administered aflibercept compared to ranibizumab (in a non-inferiority paradigm) in preventing moderate vision loss in subjects with all sub-types of neovascular AMD.
- Moderate vision loss is defined as loss of fewer than 15 letters in ETDRS letter score compared to Baseline.

VIEW #1 and VIEW #2

- On day 1, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:
 - 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
 - 0.5 mg ranibizumab administered every 4 weeks (RQ4)

VIEW #1 and VIEW #2

- 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.

VIEW #1 and VIEW #2

- The entire study duration is approximately 2 years (96 weeks plus the recruitment period).
- During the second year of treatment, sham injections will not be given.

VIEW #1 and VIEW #2

- 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. Therefore, patients will get drug every 4-12 weeks.

VIEW #1 and VIEW #2

- The pre-specified dosing 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 letters 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

Inclusion Criteria

- Signed informed consent
- Men and women ≥ 50 years of age
- Active primary subfoveal CNV lesion secondary to AMD, including juxtafoveal lesions that affected the fovea as evidenced by FA in the study eye
- CNV must be at least 50% of total lesion size
- ETDRS BCVA: 20/40-20/320 in the study eye
- Willing, committed, and able to return for all clinic visits and completed all study-related procedures
- Understand and willing to sign the ICF

Protocol Defined Analysis Populations

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

Protocol Defined Analysis Populations

- Per protocol:
 - 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 was one that may affect the interpretation of study results (i.e. missing two consecutive injections before administration of the 9th injection).

Treatment Failure

- A treatment failure was 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 : Patient Disposition

	RQ4	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 (PP)	269	285	270	265

VIEW #2 : Patient Disposition

	RQ4	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 (PP)	269	274	268	270

Primary Efficacy Endpoint

- Primary efficacy variable:
 - The proportion of subjects who maintained vision at Week 52

Primary Efficacy Endpoint

- The primary analysis is an evaluation of the non-inferiority of aflibercept 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: aflibercept 2mg q4 weeks versus ranibizumab
 - Comparison 2: aflibercept 0.5mg q4 weeks versus ranibizumab
 - Comparison 3: aflibercept 2mg q8 weeks versus ranibizumab

Primary Efficacy Endpoint

- The non-inferiority margin in individual VIEW #1 and VIEW #2 studies was 10%.
- Aflibercept 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.

Primary Efficacy Endpoint

- Once the non-inferiority was demonstrated, the superiority of aflibercept to ranibizumab was examined. Aflibercept was considered to be superior to ranibizumab if the confidence interval of the difference entirely lay below 0.
- A subject who withdrew from the study before Week 36 due to treatment failure was considered a non-responder; otherwise the last observation carried forward (LOCF) approach was used to impute missing data in this primary efficacy analysis.

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

	RQ4 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)

	RQ4 N=269	2Q4 N=285	0.5Q4 N=270	2Q8 N=265
Subjects With Maintained vision at Week 52	243 (94.9%)	260 (94.9%)	241 (96.4%)	237 (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)

	RQ4 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)

	RQ4 N=261	2Q4 N=263	0.5Q4 N=257	2Q8 N=264
Subjects With Maintained vision at Week 52	246 (94.3%)	251 (95.4%)	248 (96.5%)	253 (95.8%)
Difference (%) (95.1% CI)		-1.2 (-5.0, 2.6)	-2.3 (-5.9, 1.4)	-1.6 (-5.3, 2.2)

Primary Efficacy Endpoint

- The two studies found all dosing regimens of aflibercept to be non-inferior to ranibizumab.
- Neither study found any of the aflibercept doses to be superior to ranibizumab.

Secondary Endpoint: 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)

Secondary Endpoint: 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	2Q8N=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)

Safety

- The main support of safety for aflibercept came from VIEW #1 and VIEW #2.

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

	RQ4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
Mean Number of Injections During the First Year Including Sham (sd)	12.1 (2)	12.5 (1)	12.1 (2)	12.0 (2)
Mean Number of Injections During the First Year Excluding Sham (sd)	12.1 (2)	12.5 (1)	12.1 (2)	7.5 (1)
Mean Total Amount of Study Medication During the First Year in mg (sd)	6.0 (1)	24.9 (2)	6.0 (1)	14.9 (2)

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

	RQ4 N=291	2Q4 N=309	0.5Q4 N=297	2Q8 N=307
Mean Number of Injections During the First Year Including Sham (sd)	12.7 (1)	12.6 (1)	12.7 (1)	12.6 (1)
Mean Number of Injections During the First Year Excluding Sham (sd)	12.7 (1)	12.6 (1)	12.7 (1)	7.7 (1)
Mean Total Amount of Study Medication During the First Year in mg (sd)	6.2 (1)	24.4 (4)	6.2 (1)	15.1 (3)

VIEW #1: Deaths

- In VIEW #1 there were a 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 were 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.

VIEW #1: Nonfatal Serious Adverse Events

	RQ4 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%)
Number of subjects with at least 1 non-ocular SAE	57 (18.8%)	40 (13.2%)	50 (16.4%)	51 (16.8%)

VIEW #1: Nonfatal Serious Adverse Events

Ocular

- The most common ocular SAEs were:
 - Endophthalmitis (6 patients)
 - Reduced visual acuity (5 patients)
 - Retinal hemorrhage (4 patients)

VIEW #1: Nonfatal Serious Adverse Events Non-Ocular

- The most common non-ocular SAEs were:
 - Infections (44 patients)
 - Cardiac (42 patients)
 - Neoplasms (38 patients)

VIEW #2: Nonfatal Serious Adverse Events

	RQ4 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%)
Number of subjects with at least 1 non-ocular SAE	26 (8.9%)	36 (11.7%)	37 (12.5%)	38 (12.2%)

VIEW #2: Nonfatal Serious Adverse Events

Ocular

- The most common ocular SAEs were:
 - Visual acuity reduced (8 patients)
 - Retinal hemorrhage (5 patients)
 - Cataract (3 patients)

- Endophthalmitis (0 patients)

VIEW #2: Nonfatal Serious Adverse Events Non-Ocular

- The most common non-ocular SAEs were:
 - Cardiac disorders (31 patients)
 - Neoplasms (20 patients)
 - Infections (18 patients)

VIEW #1: Disposition

	RQ4	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 within first year	22	11	27	27
AE	4	3	5	4
Death	3	1	2	7
Withdrawal by subject	10	5	7	8
Protocol deviation	3	0	3	1
Lost to f/u	1	2	4	4
Treatment failure	0	0	2	2
Other	1	0	4	1

VIEW #2: Disposition

	RQ4	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 within first year	27	32	37	29
AE	2	6	8	9
Death	1	3	2	1
Withdrawal by subject	11	15	13	11
Protocol deviation	2	1	1	0
Lost to f/u	4	1	2	2
Treatment failure	0	0	1	1
Other	7	6	10	5

Adverse Events: VIEW #1

- The most common treatment emergent ocular AEs were:
 - Conjunctival hemorrhage
 - Vitreous floaters
 - Eye pain

Adverse Events: VIEW #2

- The most common treatment emergent ocular AEs were:
 - Visual acuity reduced
 - Conjunctival hemorrhage
 - Retinal hemorrhage

VIEW #2: Special Safety Study

Nasomucosal examination (ENT sub-study)

- A subset of 160 subjects in VIEW #2 were additionally examined by an ENT specialist and had a nasal endoscopy.
- 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: Special Safety Study

Nasomucosal examination (ENT sub-study)

- A careful endoscopy of the nasal airways with a standardized documentation of findings comprised the rhinological investigation at Visit 2 (baseline nasal endoscopy).
- 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 repeat nasal endoscopy was performed.

VIEW #2: Special Safety Study

Nasomucosal examination (ENT sub-study)

	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

VIEW #2: Special Safety Study

Nasomucosal examination (ENT sub-study)

	R0.5Q4 N=37	2Q4 N=42	0.5Q4 N=37	2Q8 N=44
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 infection	1	1	1	4
Rhinitis	2	0	1	1
Viral rhinitis	0	0	1	1
Acute tonsillitis	1	0	0	0

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

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

	R0.5Q4 N=304	2Q4 N=304	0.5Q4 N=304	2Q8 N=303
<i>Any Visit</i>	13	13	7	13

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

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

VIEW #1: Proportion of Subjects With ≥ 10 mmHg 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 ≥ 10 mmHg 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

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.

Questions for the Advisory Committee

- Do you think adequate safety and efficacy for aflibercept injection has been demonstrated for the treatment of neovascular AMD?
 - If yes, on which study(ies) are you basing your decision?
 - If not, what additional study(ies) should be performed? Do you have any suggestions regarding trial design?

Questions for the Advisory Committee

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

Questions for the Advisory Committee

- Elevations in IOP following repeated dosing of VEGF-inhibitors have been reported in the literature and are seen in low frequency in the trials of aflibercept. Do you have recommendations regarding ways to handle the issue?

Questions for the Advisory Committee

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

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Sonal D. Wadhwa, MD
US Food and Drug Administration
Medical Officer
June 17, 2011

Study VGFT-OD-0702

- 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.

Study VGFT-OD-0702

- 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)

Study VGFT-OD-0702

- VGFT-OD-0702 was a single-masked (to the subject), randomized, multi-center clinical study.
- 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 μ L injection volume from a PFS (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).
 - 2 mg VEGF Trap-Eye PRN in a 50 μ L injection volume from a Vial (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).