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# SUBGROUP ANALYSES - PRIMARY EFFICACY VARIABLE

Table 6.1.4.2-7 Subgroup Analysis for the Proportion Losing <15 Letters in Visual Acuity in the Study Eye at 12 Months Compared with Baseline at a Starting Test Distance of 4 Meters: Randomized Subjects

|                           | Age < 75 Years |                                |               |                | Age ≥ 75 Years                |               |  |  |
|---------------------------|----------------|--------------------------------|---------------|----------------|-------------------------------|---------------|--|--|
|                           | 43             | 37                             | 55            | 99             | 97                            | 85            |  |  |
| N                         |                |                                |               |                |                               |               |  |  |
| n (%)                     | 26 (61.9%)     | 35 (91.2%)                     | 53 (98.1%)    | 67 (67.7%)     | 91 (93.8%)                    | 83 (97.6%)    |  |  |
| 95% CI of the %           | (47.2%, 76.6%) | (91.9%, 100%)                  | (94.6%, 100%) | (58.5%, 76.9%) | (89.0%, 98.6%)                | (94.4%, 100%) |  |  |
| Difference in % (vs. PDT) |                | 35.3%                          | 36.2%         |                | 26.1%                         | 30.0%         |  |  |
|                           |                | Female                         |               |                | Male                          |               |  |  |
| N                         | 78             | 64                             | 64            | 63             | 69                            | 75            |  |  |
| n (%)                     | 51 (65.4%)     | 61 (95.3%)                     | 63 (98.4%)    | 42 (66.7%)     | 65 (64.2%)                    | 73 (97.3%)    |  |  |
| 95% CI of the %           | (54.8%, 75.9%) | (90.1%, 100%)                  | (95.4%, 100%) | (55.0%, 78.3%) | (88.7%, 99.7%)                | (93.7%, 100%) |  |  |
| Difference in % (vs. PDT) |                | 29.9%                          | 33.1%         |                | 27.5%                         | 30.7%         |  |  |
|                           |                | ≤ 44 Letters                   |               |                | ≥ 45 Letters                  |               |  |  |
| N                         | 65             | 58                             | 60            | 76             | 75                            | 78            |  |  |
| n (%)                     | 49 (75.4%)     | 55 (94.8%)                     | 58 (96.7%)    | 44 (57.9%)     | 71 (94.7%)                    | 77 (98.7%)    |  |  |
| 95% CI of the %           | (64.9%, 85.9%) | (89.1%, 100%)                  | (92.1%, 100%) | (46.8%, 69.0%) | (89.6%, 99.8%)                | (96.2%, 100%) |  |  |
| Difference in % (vs. PDT) |                | 19.4%                          | 21.3%         |                | 36.8%                         | 40.8%         |  |  |
|                           |                | Occult CNV Present at Baseline |               |                | Occult CNV Absent at Baseline |               |  |  |
| N                         | 16             | 17                             | 18            | 125            | 116                           | 121           |  |  |
| n (%)                     | 7 (43.8%)      | 15 (88.2%)                     | 18 (100%)     | 86 (68.8%)     | 111 (95.7%)                   | 118 (97.5%)   |  |  |

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|                                      | Verapamil<br>PDT<br>0.3 mg | Ranibizumab<br>PDT<br>0.3 mg | Verapamil<br>PDT<br>0.3 mg | Ranibizumab<br>PDT<br>0.3 mg |
|--------------------------------------|----------------------------|------------------------------|----------------------------|------------------------------|
| 95% CI of the %                      | (19.4%, 68.1%)             | (72.9%, 100%)                | (60.7%, 76.9%)             | (94.8%, 100%)                |
| Difference in % (vs. PDT)            | 44.5 %                     | 56.3 %                       | 26.9 %                     | 28.7 %                       |
| p-value (vs. PDT)                    | 0.0067                     | 0.0002                       | <0.0001                    | <0.0001                      |
| Baseline Lesion Size ≤ 4 DA          |                            |                              |                            |                              |
| N                                    | 125                        | 124                          | 126                        | 13                           |
| n (%)                                | 82 (65.6%)                 | 117 (94.4%)                  | 11 (68.8%)                 | 9 (100%)                     |
| 95% CI of the %                      | (57.3%, 73.9%)             | (90.3%, 98.4%)               | (46.0%, 91.5%)             | (100%, 100%)                 |
| Difference in % (vs. PDT)            | 28.8 %                     | 32.8 %                       | 31.3 %                     | 23.6 %                       |
| p-value (vs. PDT)                    | <0.0001                    | <0.0001                      | 0.0608                     | 0.1194                       |
| With Prior Laser Photocoagulation    |                            |                              |                            |                              |
| N                                    | 19                         | 19                           | 20                         | 114                          |
| n (%)                                | 11 (57.9%)                 | 19 (100.0%)                  | 82 (67.2%)                 | 107 (93.9%)                  |
| 95% CI of the %                      | (35.7%, 80.1%)             | (100%, 100%)                 | (58.9%, 75.5%)             | (89.5%, 98.3%)               |
| Difference in % (vs. PDT)            | 42.1 %                     | 42.1 %                       | 26.6 %                     | 30.3 %                       |
| p-value (vs. PDT)                    | 0.0015                     | 0.0011                       | <0.0001                    | <0.0001                      |
| With No Prior Laser Photocoagulation |                            |                              |                            |                              |
| N                                    | 19                         | 19                           | 20                         | 114                          |
| n (%)                                | 11 (57.9%)                 | 19 (100.0%)                  | 82 (67.2%)                 | 107 (93.9%)                  |
| 95% CI of the %                      | (35.7%, 80.1%)             | (100%, 100%)                 | (58.9%, 75.5%)             | (89.5%, 98.3%)               |
| Difference in % (vs. PDT)            | 42.1 %                     | 42.1 %                       | 26.6 %                     | 30.3 %                       |
| p-value (vs. PDT)                    | 0.0015                     | 0.0011                       | <0.0001                    | <0.0001                      |

Note: The LOCF was used to impute missing data. The 95% CIs were based on normal approximation. p-values were from the Pearson Chi Square test.

#### Reviewer's Comment:

The approximately 30% treatment effect was maintained and was statistically significant to the  $p < 0.0001$  level in all except for a few subgroups likely due to the small number of subjects in those subgroups.

In patients with a baseline lesion size of  $> 4$  disc areas, only the ranibizumab 0.3-mg dose achieved statistical significance versus verapamil PDT,  $p = 0.0242$ , perhaps due to the small number of subjects or worse disease. In this subgroup, the ranibizumab pooled group was significant with a p-value of 0.0199. Similar results were seen in the subgroups with occult CNV present at baseline and with prior laser photocoagulation.

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#### 6.1.5 Clinical Microbiology

This is not an antimicrobial. Not applicable.

#### 6.1.6 Efficacy Conclusions

The submitted Phase 3 studies in BLA 125156 Lucentis (ranibizumab injection) demonstrate the efficacy for the use of ranibizumab 0.5-mg in the treatment of neovascular age-related macular degeneration.

These studies both demonstrated an approximately 30% treatment effect of ranibizumab 0.3-mg and 0.5-mg compared to sham and verteporfin PDT, respectively, for the primary efficacy endpoint, the proportion of subjects with a loss of fewer than 15 letters in the best corrected visual acuity score at Month 12 compared with baseline.

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## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

The Phase 3 studies presented in this Biologics License Application, FVF2587g and FVF2598g, included 754 safety evaluable patients. In Study FVF2598g, subjects were followed monthly from Day 0 through Month 12 and received an average 12 of a total 13 possible intravitreal ranibizumab injections. The number of treatments received was slightly lower for the sham-injection group compared with the ranibizumab groups. There was no imputation of missing values due to patient discontinuation or missed visits performed in the safety data set. In Study FVF2587g, subjects were followed monthly as well. The mean number of injections in the ranibizumab and sham intravitreal injection groups was approximately 12 for each group.

Safety was assessed through the summary of ocular and non-ocular adverse events, serious adverse events, ocular assessments, deaths, laboratory test results, vital signs, and antibodies to ranibizumab. Safety analyses included all subjects who received at least one ranibizumab or sham injection. Unless specified otherwise, safety analyses were performed for the safety-evaluable subjects. Subjects were analyzed according to the actual treatment received. Safety summaries for this Clinical Study Report include data from the first treatment year.

In Study FVF2598g, the safety evaluable population was defined as randomized subjects who received at least one treatment with study drug. Treatment group assignment as follows:

- Sham: subjects randomized to the sham-injection group who received a sham injection on Day 0
- 0.3 mg Ranibizumab: subjects randomized to receive 0.3 mg ranibizumab or subjects who were randomized to sham but received a 0.3 mg injection of ranibizumab on Day 0 in error
- 0.5 mg Ranibizumab: subjects randomized to receive 0.5 mg ranibizumab or subjects who were randomized to sham but received a 0.5 mg injection of ranibizumab on Day 0 in error

In Study FVF2587g, the safety-evaluable population was defined as randomized subjects who received at least one of the following treatments: ranibizumab injection, sham intravitreal injection, active verteporfin PDT, or sham PDT with saline. Treatment groups for this population were defined according to the actual treatment received during the first treatment year.

- If a subject received only one type of active treatment (verteporfin PDT, 0.3 mg ranibizumab or 0.5 mg ranibizumab), regardless of any sham PDT or sham intravitreal injections received, the subject's treatment group was the active treatment received.
- If a subject received a combination of different active treatments, regardless of any sham PDT or sham intravitreal injections received, and one of the active treatments received

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was the treatment the subject was randomized to, the subject's treatment group was as randomized.

- If a subject received a combination of different active treatments, regardless of any sham PDT or sham intravitreal injection received, and none of the active treatments received was the treatment the subject was randomized to, the subject's treatment group was the first active treatment received.
- If a subject did not receive any active treatment but received any combination of sham PDT or sham intravitreal injection, the subject's treatment group was as randomized.

In Study FVF2598g, the most common ocular adverse events in the study eye reported more frequently in each of the ranibizumab groups than in the corresponding control groups in both studies were conjunctival hemorrhage, eye pain, increased IOP, retinal disorder, and vitreous floaters. Many of these adverse events appear to be related to the conjunctival anesthetic or intravitreal injection procedures.

Key serious ocular adverse events of endophthalmitis, intraocular inflammation, retinal detachment, retinal tear, increased IOP, and traumatic cataract were all uncommon in ranibizumab-treated subjects (reported in < 1% of subjects for each event). Per injection rates for the serious adverse events of endophthalmitis, intraocular inflammation, retinal detachment, and traumatic cataract were all very low ( $\leq 0.12\%$  per injection in each dose group).

A trend in intraocular inflammation adverse events was observed, with rates of approximately 10%–15% in the ranibizumab groups compared with rates of approximately 3% or 10% in the verteporfin PDT or sham-control groups, respectively. However, the reported intraocular inflammation adverse events were generally mild in severity. The incidence of intraocular inflammation adverse events was consistent with the results based on slitlamp examination.

As expected with a drug injected intravitreally, there was a small trend in increased IOP adverse events toward higher rates in the ranibizumab groups than in the control groups, with no difference in frequency or severity observed between the two doses. Most of these events were mild to moderate in severity.

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#### 7.1.1 Deaths

Three deaths occurred during the first treatment year of Study FVF2598g. One subject in the 0.3 mg ranibizumab group died from a heart attack. The other two subjects were both in the ranibizumab 0.5 mg group; 1 subject died as a result of a small bowel infarct and the other died from chronic asthma / chronic obstructive pulmonary disease (COPD).

Seven deaths occurred during the first treatment year of Study FVF2587g.

Table 7.1.1-1 Deaths Occurring during Phase 3 Studies

| Primary Cause           | Study FVF2587g (N=140) |          |          |          |          |          |
|-------------------------|------------------------|----------|----------|----------|----------|----------|
|                         | Ranibizumab            |          |          |          |          |          |
|                         | 0.3 mg                 | 0.5 mg   | 1.0 mg   | 2.0 mg   | 3.0 mg   | 4.0 mg   |
| Total                   | 0                      | 1 (0.4%) | 2 (0.6%) | 2 (1.4%) | 3 (2.2%) | 2 (1.4%) |
| Cardiac Arrest          | 0                      | 0        | 0        | 1 (0.7%) | 1 (0.7%) | 0        |
| Cardiac Failure         | 0                      | 0        | 0        | 0        | 0        | 1 (0.7%) |
| COPD                    | 0                      | 0        | 1 (0.4%) | 1 (0.7%) | 0        | 0        |
| Myocardial infarction   | 0                      | 1 (0.4%) | 0        | 0        | 0        | 0        |
| Respiratory Arrest      | 0                      | 0        | 0        | 0        | 1 (0.7%) | 0        |
| Small bowel infarct     | 0                      | 0        | 1 (0.4%) | 0        | 0        | 0        |
| Viral Syndrome          | 0                      | 0        | 0        | 0        | 1 (0.7%) | 0        |
| Worsened of chronic CHF | 0                      | 0        | 0        | 0        | 0        | 1 (0.7%) |

#### Reviewer's Comment:

*There were considerably more deaths in the FVF2587g trial though there were no imbalances in the causes or association to treatment noted.*

*The deaths were not considered to be related to therapy.*

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## 7.1.2 Other Serious Adverse Events

Table 7.1.2-1 Study FVF2598g  
Serious Ocular Adverse Events in the Study Eye during the First Treatment Year  
Safety Evaluable Subjects

| Study ID      | Subject ID | Event                                                       | Count   | Disposition          |
|---------------|------------|-------------------------------------------------------------|---------|----------------------|
| S08215        | 104005     | 30 letter loss of vision                                    | 99      | None                 |
| S08037        | 105001     | Serous hemorrhagic macular detachment                       | 303     | None                 |
| S07441        | 107003     | Subretinal hemorrhage                                       | 63      | Dose held            |
| S08216        | 108006     | 30 letter loss of vision - Worsened CNV                     | 246     | None                 |
| S08201        | 118004     | Cerebrovascular accident                                    | 319     | None                 |
| S08130        | 125006     | 30 letter loss of vision - Worsened AMD                     | 32      | None                 |
| S08220        | 143005     | 30 letter loss of vision - Worsened AMD                     | 239     | Dose held            |
| S08212        | 144002     | 30 letter loss of vision - Worsened AMD                     | 94      | Dose held, PDT       |
| S08366        | 148001     | 30 letter loss of vision - Worsened AMD                     | 155     | Dose held            |
| S08133        | 164002     | Progression of AMD                                          | 57      | Dose held, D/C study |
| S02796        | 185005     | 30 letter loss of vision - Worsened AMD                     | 127     | None                 |
| S02201        | 188006     | 30 letter loss of vision - Worsened AMD                     | 62      | None                 |
| 0.3 mg/0.5 ml |            |                                                             |         |                      |
| S07348        | 101001     | 30 letter loss of vision - Worsened AMD                     | 126     | None                 |
| S08127        | 102005     | 30 letter loss of vision                                    | 122     | Dose held            |
| S08217        | 123002     | Iridocyclitis                                               | 33      | None                 |
| S06531        | 126002     | Retinal tear                                                | 58      | Dose held, Procedure |
| S08246        | 131003     | 30 letter loss of vision - Subretinal fibrosis              | 127     | None                 |
| S08246        | 131013     | Increased intraocular pressure                              | 239     | None                 |
| S08208        | 141014     | 30 letter loss of vision - Vit. hemorrhage                  | 84      | Dose held            |
| S08220        | 143011     | Endophthalmitis                                             | 270     | Meds / Surgery       |
|               | 143018     | 30 letter loss of vision - Worsened AMD                     | 60      | None                 |
| S08189        | 160001     | Iridocyclitis                                               | 94      | Study drug d/c'd     |
| S00399        | 162002     | Retinal hemorrhage, Depression                              | 15      | D/C Study            |
| S08131        | 179002     | 30 letter loss of vision - Worsened AMD                     | 148     | None                 |
| S08125        | 183001     | 30 letter loss of vision - Worsened AMD                     | 183     | None                 |
| S08165        | 184001     | RPE Tear / Detachment                                       | 30      | None                 |
| S08252        | 193001     | Corneal abrasion                                            | 343     | None                 |
| 0.5 mg/0.5 ml |            |                                                             |         |                      |
| S07441        | 107008     | RPE Tear / Detachment                                       | 33      | Dose held            |
| S08110        | 117002     | Hyphema                                                     | 29      | Meds / AC Tap        |
| S08246        | 131012     | Increased intraocular pressure                              | 183     | Meds / AC Tap        |
| S06530        | 138002     | Iridocyclitis - Recurrent                                   | 37, 119 | Study drug d/c'd     |
| S08208        | 141005     | Accidental penetration of lens with needle during injection | 69      | Cataract extraction  |
|               | 141016     | Fat embolism, retinal artery                                | 204     | Hospitalization      |
| S08220        | 143017     | Uveitis                                                     | 62      | Study drug d/c'd     |
| S08150        | 15306      | 30 letter loss of vision - Unexplained                      | 308     | Dose held            |
| S08083        | 163004     | Endophthalmitis                                             | 66      | Meds / Surgery       |
| S00266        | 167007     | Incorrect route of administration                           | 240     | Dose held            |

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|        |        |                                                |     |       |
|--------|--------|------------------------------------------------|-----|-------|
| S08211 | 170009 | Round pupil hole                               | 8   | Laser |
| S08252 | 193003 | 30 letter loss of vision - Worsened AMD        | 254 | None  |
| S03675 | 200004 | 30 letter loss of vision - Vitreous hemorrhage | 210 | None  |

Table 7.1.2-2 Study FV#2587g  
Serious Ocular Adverse Events in the Study Eye during the First Treatment Year  
Safety Evaluable Subjects

|        |        |                                                     |          |                            |
|--------|--------|-----------------------------------------------------|----------|----------------------------|
| S08214 | 321011 | 30 letter loss of vision - Retinal hemorrhage       | 43       | None                       |
| S08130 | 335003 | 30 letter loss of vision - Worsened AMD             | 184      | None                       |
| S08222 | 344002 | 30 letter loss of vision - Unexplained              | 29       | None                       |
| S08263 | 363002 | 30 letter loss of vision - Worsened AMD             | 31       | None                       |
| S08255 | 365001 | 30 letter loss of vision - Worsened AMD             | 186, 235 | None                       |
| S09325 | 381008 | Retinal detachment                                  | 114, 189 | Surgery, Study drug d/c'd  |
| S07441 | 303001 | Retinal detachment                                  | 58       | Surgery, Study drug d/c'd  |
| S08215 | 305002 | 30 letter loss of vision - Worsened AMD             | 126, 169 | None                       |
| S06444 | 319007 | Vitreous hemorrhage                                 | 276      | None                       |
| S08214 | 321006 | 30 letter loss of vision - Unexplained              | 295      | None                       |
| S08325 | 354006 | Medication Error                                    | 302      | None                       |
| S08314 | 364002 | Incorrect injection procedure - no lidocaine admin. | 338      | None                       |
| S08235 | 304005 | Medication Error                                    | 367      | None                       |
| S08146 | 326001 | Occludable narrow angle                             | 104      | Iridotomy                  |
| S08596 | 334009 | Corneal abrasion                                    | 29       | Medication                 |
| S08211 | 339004 | 30 letter loss of vision - Submacular hemorrhage    | 95       | Dose held, Surgery         |
| S08248 | 340003 | 30 letter loss of vision - Worsened AMD             | 92       | None                       |
| S08207 | 341003 | Endophthalmitis                                     | 122      | Dose held, Procedure       |
| S08234 | 349006 | Corneal abrasion                                    | 296      | None                       |
|        | 349006 | Afferent pupillary defect                           | 357      | Study drug and Study d/c'd |
| S09308 | 389001 | Recurrent uveitis                                   | 231, 270 | Study drug and Study d/c'd |

<sup>1</sup> Subject's vision fluctuated throughout study and was suspected of peaking at certain visits.

**Reviewer's Comment:**

The most frequent cause of a serious adverse event was the loss of 30 letters of vision which was usually due to progression of macular degeneration. The greatest number of these occurrences was in the sham- or Verteporfin PDT- treated groups, followed by the ranibizumab 0.3mg- and 0.5 mg-treated groups, respectively.

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**Table 7.1.2-3 Study FVF2598g**  
**Serious Ocular Adverse Events in the Fellow Eye during the First Treatment Year**  
**Safety Evaluable Subjects**

| Study ID | Subject ID | Event                                   | Count | Outcome         |
|----------|------------|-----------------------------------------|-------|-----------------|
| S07847   | I15009     | 30 letter loss of vision – New CNVM     | 306   | Surgery - TPPV  |
|          |            | Elevated intraocular pressure – Postop  | 327   | Medications     |
| S08201   | I18004     | Visual field defect – CVA               | 319   | Hospitalization |
| S08239   | I21007     | 30 letter loss of vision – New CNVM     | 31    | None            |
| S08130   | I25008     | 30 letter loss of vision – New CNVM     | 50    | PDT, D/C Study  |
| S08249   | I36009     | 30 letter loss of vision – New CNVM     | 92    | PDT             |
|          |            | 0.3 mg/0.4 ml                           |       |                 |
| S08218   | I14005     | 30 letter loss of vision – Worsened AMD | 218   | PDT             |
| S07847   | I15002     | 30 letter loss of vision – Unexplained  | 160   | None, resolved  |
| S08248   | I40005     | Retinal detachment                      | 299   | Surgery         |
|          |            | Recurrent retinal detachment            | 341   | Surgery         |
| S08194   | I76003     | 30 letter loss of vision – Worsened AMD | 164   | PDT             |
|          |            | 0.5 mg/0.4 ml                           |       |                 |
| S08216   | I08004     | 30 letter loss of vision – New CNVM     | 66    | PDT             |
| S07439   | I12004     | 30 letter loss of vision – Unexplained  | 127   | None, resolved  |

**Table 7.1.2-4 Study FVF2587g**  
**Serious Ocular Adverse Events in the Fellow Eye during the First Treatment Year**  
**Safety Evaluable Subjects**

| Study ID | Subject ID | Event                                            | Count | Outcome              |
|----------|------------|--------------------------------------------------|-------|----------------------|
| S08314   | 364004     | Medication Error – Not fully eye injected        | 264   | None                 |
|          |            | 0.3 mg/0.4 ml                                    |       |                      |
| S08214   | 321006     | 30 letter loss of vision – Unexplained           | 337   | None                 |
| S08214   | 321013     | 30 letter loss of vision – Subretinal hemorrhage | 295   | Laser tx             |
| S08150   | 329008     | 30 letter loss of vision – Worsened AMD          | 85    | PDT                  |
| S08133   | 358003     | 30 letter loss of vision – Recurrent CNVM        | 68    | PDT, steroid injxn   |
| S09326   | 390001     | Sudden loss of vision – Blindness                | 337   | PDT                  |
|          |            | 0.5 mg/0.4 ml                                    |       |                      |
| S08220   | 302013     | 30 letter loss of vision – Worsened AMD          | 246   | PDT                  |
| S08214   | 321007     | 30 letter loss of vision – Worsened AMD          | 330   | Laser, steroid injxn |
| S08205   | 342003     | 30 letter loss of vision                         | 234   | None                 |

<sup>1</sup> Patient with short term memory loss, difficult to assess vision.

**Reviewer's Comment:**

*The most frequent cause of a serious adverse event in the fellow eye was the loss of 30 letters of vision due to progression of macular degeneration in both studies regardless of treatment group.*

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Table 7.1.2-5  
Non-Ocular Serious Adverse Events during the First Treatment Year (Occurring in ≥ 2 Subjects in Any Group)  
Safety Evaluable Subjects – Study FV2598g and Study FV2587g

|                                         | 39 (16.5%)            | 43 (18.1%)      | 44 (18.4%)      | 28 (19.6%)      | 20 (14.6%)      | 28 (20.8%)      |
|-----------------------------------------|-----------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <b>TOTAL<sup>a</sup></b>                | <b>4 (1.7%)</b>       | <b>7 (2.9%)</b> | <b>4 (1.7%)</b> | <b>2 (1.4%)</b> | <b>4 (2.9%)</b> | <b>4 (2.9%)</b> |
| Pneumonia                               | 1 (0.4%)              | 2 (0.8%)        | 3 (1.3%)        | 0               | 0               | 0               |
| Dysrhythmias                            | 4 (1.7%)              | 0               | 1 (0.4%)        | 0               | 0               | 0               |
| Syncope                                 | 4 (1.7%)              | 0               | 1 (0.4%)        | 0               | 3 (2.2%)        | 0               |
| Coronary artery disease                 | 3 (1.3%)              | 1 (0.4%)        | 1 (0.4%)        | 0               | 0               | 0               |
| Cardiac failure, congestive             | 2 (0.8%)              | 3 (1.3%)        | 0               | 0               | 0               | 2 (1.4%)        |
| Chest pain                              | 1 (0.4%) <sup>b</sup> | 1 (0.4%)        | 3 (1.3%)        | 0               | 0               | 0               |
| Cerebrovascular accident                | 3 (1.3%)              | 1 (0.4%)        | 0               | 0               | 0               | 0               |
| Cellulitis                              | 0                     | 3 (1.3%)        | 1 (0.4%)        | 0               | 0               | 0               |
| Hip fracture                            | 1 (0.4%)              | 1 (0.4%)        | 2 (0.8%)        | 0               | 0               | 0               |
| Asthma                                  | 2 (0.8%)              | 1 (0.4%)        | 0               | 0               | 1 (0.7%)        | 0               |
| Brain metastasis                        | 2 (0.8%)              | 1 (0.4%)        | 0               | 0               | 0               | 2 (1.4%)        |
| Lung metastasis, malignant              | 1 (0.4%)              | 1 (0.4%)        | 0               | 0               | 0               | 0               |
| COPD Exacerbation                       | 0                     | 0               | 2 (0.8%)        | 2 (1.4%)        | 0               | 3 (2.1%)        |
| COPD                                    | 2 (0.8%)              | 0               | 0               | 0               | 0               | 3 (2.1%)        |
| Abdominal pain, upper                   | 0                     | 0               | 0               | 0               | 0               | 0               |
| Non-cardiac chest pain                  | 0                     | 0               | 2 (0.8%)        | 0               | 0               | 0               |
| Osteoarthritis                          | 2 (0.8%)              | 0               | 0               | 0               | 0               | 0               |
| Renal cell carcinoma, stage unspecified | 2 (0.8%)              | 0               | 0               | 0               | 0               | 0               |
| Transient ischemic attack <sup>c</sup>  | 0                     | 0               | 2 (0.8%)        | 0               | 0               | 0               |
| Subdural hematoma                       | 0                     | 0               | 0               | 0               | 2 (1.5%)        | 0               |

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence. Events which occurred more frequently in the 0.5-mg group of either study are highlighted.

<sup>a</sup> Represents the number of subjects with at least one non-ocular serious adverse event. <sup>b</sup> The sham-treated subject (118004) who experienced a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event. <sup>c</sup> Included one case reported as a cerebral ischemia.

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**Reviewer's Comment:**

*The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus either control are highlighted.  
In the FFF2598g study, serious non-ocular events were evenly distributed across the ranibizumab treated groups; but, slightly less frequent in the sham treated group.*

*In the FFF2587g study, serious non-ocular events occurred with approximately equal frequency in the verteporfin PDT and ranibizumab 0.5 mg treated groups. The frequency was somewhat less in the ranibizumab 0.3mg- treated group.*

**7.1.3 Dropouts and Other Significant Adverse Events**

The case report forms of all subjects who discontinued study participation were evaluated. Refer to Table 6.1.3.1-7 and Table 6.1.3.2-7 for details.

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### 7.1.3.1 Overall profile of dropouts

Table 7.1.3.1-1 Subject Disposition and Reasons for Discontinuation: Randomized Subjects

|                                                             | 238         | 238         | 238         | 240         | 143         | 140         | 140         |
|-------------------------------------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Randomized                                                  | 238         | 238         | 238         | 239         | 143         | 137         | 140         |
| Received ranibizumab or sham injection                      | 236 (99.2%) | 238 (100%)  | 238 (100%)  | 239 (100%)  | 143 (100%)  | 137 (97.9%) | 140 (100%)  |
| Received verteporfin or sham PDT                            | ---         | ---         | ---         | ---         | 143 (100%)  | 137 (97.9%) | 140 (100%)  |
| Completed Month 12 <sup>a</sup>                             | 212 (89.1%) | 226 (95.0%) | 226 (94.2%) | 226 (94.2%) | 127 (88.8%) | 128 (91.4%) | 131 (93.6%) |
| Discontinued treatment <sup>b</sup> prior to Month 12       | 31 (13.0%)  | 10 (4.2%)   | 11 (4.6%)   | 11 (4.6%)   | 14 (9.8%)   | 13 (9.3%)   | 9 (6.4%)    |
| Death                                                       | 0           | 1 (0.4%)    | 1 (0.4%)    | 1 (0.4%)    | 1 (0.7%)    | 3 (2.1%)    | 2 (1.4%)    |
| Adverse Event                                               | 6 (2.5%)    | 3 (1.3%)    | 5 (2.1%)    | 5 (2.1%)    | 6 (4.2%)    | 3 (2.1%)    | 4 (2.9%)    |
| Lost to follow-up                                           | 2 (0.8%)    | 0           | 0           | 0           | 1 (0.7%)    | 0           | 1 (0.7%)    |
| Subject's Decision                                          | 15 (6.3%)   | 6 (2.5%)    | 4 (1.7%)    | 4 (1.7%)    | 4 (2.8%)    | 4 (2.9%)    | 2 (1.4%)    |
| Physician's Decision                                        | 2 (0.8%)    | 0           | 1 (0.4%)    | 1 (0.4%)    | 1 (0.7%)    | 2 (1.4%)    | 0           |
| Subject non-compliance                                      | 0           | 0           | 0           | 0           | 0           | 1 (0.7%)    | 0           |
| Subject's condition mandated other therapeutic intervention | 6 (2.5%)    | 0           | 0           | 0           | 1 (0.7%)    | 0           | 0           |

<sup>a</sup> Defined as having a visual acuity score in the study eye at Month 12. Data from subjects who missed the Month 12 visit but stayed in the study for the second year were not counted.<sup>b</sup> Two subjects were discontinued from the study at Month 12 after assessments.

### Reviewer's Comment:

*In both studies, the sham injection and verteporfin PDT groups had higher rates of study dropout and treatment discontinuation than the ranibizumab groups.*

*Approximately 50% of the treatment discontinuations were due to subject decision.*

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### 7.1.3.2 Adverse events associated with dropouts

Treatment discontinuation and study dropout was most frequently associated with the subject's decision with no change in vision from baseline, subject's loss of vision and progression of age-related macular degeneration.

**Table 7.1.3.2-1 Ocular Adverse Events in the Study Eye Leading to Discontinuation of Study or Treatment during the First Treatment Year: Safety Evaluable Subjects**

|                                  | MedORA Treatment Group |                 | Sham Treatment Group |                 | Total            |                 |
|----------------------------------|------------------------|-----------------|----------------------|-----------------|------------------|-----------------|
|                                  | Number                 | %               | Number               | %               | Number           | %               |
| <b>TOTAL*</b>                    | <b>8 (3.4%)</b>        | <b>3 (1.3%)</b> | <b>4 (1.7%)</b>      | <b>1 (0.7%)</b> | <b>12 (5.1%)</b> | <b>4 (3.9%)</b> |
| Chorioretinal neovascularization | 0                      | 0               | 1 (0.4%)             | 0               | 1 (0.7%)         | 0               |
| Choroidal neovascularization     | 4 (1.7%)               | 0               | 0                    | 0               | 4 (3.4%)         | 0               |
| Conjunctivitis allergic          | 0                      | 0               | 1 (0.4%)             | 0               | 1 (0.7%)         | 0               |
| Conjunctivitis bacterial         | 0                      | 0               | 0                    | 0               | 0                | 1 (0.7%)        |
| Corneal deposits                 | 0                      | 0               | 1 (0.4%)             | 0               | 1 (0.7%)         | 0               |
| Eye pain                         | 0                      | 0               | 1 (0.4%)             | 0               | 1 (0.7%)         | 0               |
| Iritis                           | 0                      | 0               | 0                    | 0               | 0                | 0               |
| Iridocyclitis                    | 0                      | 0               | 2 (0.8%)             | 0               | 2 (1.7%)         | 0               |
| Macular degeneration             | 0                      | 0               | 1 (0.4%)             | 0               | 1 (0.7%)         | 0               |
| Ocular hyperemia                 | 3 (1.3%)               | 0               | 0                    | 0               | 3 (2.5%)         | 0               |
| Pupillary reflex impaired        | 0                      | 0               | 0                    | 0               | 0                | 1 (0.7%)        |
| Retinal detachment <sup>b</sup>  | 0                      | 0               | 0                    | 0               | 0                | 0               |
| Retinal hemorrhage               | 2 (0.8%)               | 1 (0.4%)        | 0                    | 0               | 3 (2.5%)         | 0               |
| Uveitis                          | 0                      | 0               | 1 (0.4%)             | 0               | 1 (0.7%)         | 0               |
| Vision blurred                   | 0                      | 0               | 0                    | 0               | 0                | 0               |
| Vitreous detachment              | 2 (0.8%)               | 0               | 0                    | 0               | 2 (1.7%)         | 0               |

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence. \* Represents the number of subjects with at least one ocular adverse event in the study eye that led to discontinuation of study or treatment. b Both events were idiopathic retinal detachment.

### Reviewer's Comment:

In Study FIV2598g, the adverse events which led to discontinuation of subjects in the sham-injection group were primarily related to progression of age-related macular degeneration. The adverse event which led to discontinuation in ranibizumab treated subjects most frequently in both studies was intraocular inflammation (iritis, iridocyclitis, and uveitis).

Ocular adverse events that led to discontinuation in the ranibizumab groups were generally those associated with intravitreal injections.

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**Table 7.1.3.2-2 Non-Ocular Adverse Events in the Study Eye Leading to Discontinuation of Study or Treatment during the First Treatment Year: Safety Evaluable Subjects**

[illegible]

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.

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a Represents the number of subjects with at least one non-ocular adverse event in the study eye that led to discontinuation of study or treatment.

#### Reviewer's Comment:

*No pattern of non-ocular adverse events leading to study or treatment discontinuation was noted in either study. The non-ocular adverse events reported were conditions commonly seen in an elderly population.*

#### 7.1.3.3 Other significant adverse events

**Table 7.1.3.3-1 Serious Adverse Events Potentially Related to Systemic VEGF Inhibition during the First Treatment Year:  
 Studies FV72598g and FV72587g**

| TOTAL*                              | 2 (0.4%) | 8 (3.4%) | 9 (3.5%) | 3 (2.1%) | 4 (2.9%) | 8 (5.7%) |
|-------------------------------------|----------|----------|----------|----------|----------|----------|
| Hypertension events                 | 0        | 1 (0.4%) | 0        | 0        | 0        | 0        |
| Arterial thromboembolic events      | 2 (0.8%) | 5 (2.1%) | 8 (3.3%) | 2 (1.4%) | 2 (1.4%) | 4 (2.9%) |
| Non-ocular hemorrhages              | 0        | 1 (0.4%) | 0        | 0        | 2 (1.5%) | 3 (2.1%) |
| Other potentially associated events | 0        | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |

Note: Multiple occurrences of the same type of event for a subject were counted once in the overall incidence.

#### Reviewer's Comment:

*In the two phase 3 studies, a small trend in the occurrence of serious adverse events potentially related to systemic VEGF inhibition was noted at Month 12, particularly in the ranibizumab 0.5-mg dose group. This reflects trends in serious arterial thromboembolic events and, to a lesser extent, in serious non-ocular hemorrhages (but not in serious hypertension or proteinuria). No imbalance in overall adverse events potentially related to systemic VEGF inhibition was observed among treatment groups.*

Differing definitions, assessment methods, and reporting of arterial thromboembolic events makes there analysis challenging. The sponsor applied the Antiplatelet Trialists' Collaboration (APTC) classification (Antiplatelet Trialists' Collaborations 1994) to the adverse events which mitigates some of these issues by focusing on a more restricted but well-defined spectrum of serious adverse events: vascular deaths (including deaths of unknown cause), nonfatal myocardial infarction, nonfatal ischemic stroke, and nonfatal hemorrhagic stroke.

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Table 7.1.3.3-2 APTC Arterial Thromboembolic Events during the First Treatment Year:  
Studies FYF2598g and FYF2587g

| Event                                                                                                                                      | Study FYF2598g |        | Study FYF2587g |        | Total |        |
|--------------------------------------------------------------------------------------------------------------------------------------------|----------------|--------|----------------|--------|-------|--------|
|                                                                                                                                            | n              | %      | n              | %      | n     | %      |
| TOTAL                                                                                                                                      | 2              | (0.8%) | 3              | (1.3%) | 5     | (2.1%) |
| Vascular deaths                                                                                                                            | 0              |        | 1              | (0.4%) | 1     | (0.4%) |
| Nonfatal myocardial infarction                                                                                                             | 1              | (0.4%) | 1              | (0.4%) | 2     | (0.8%) |
| Nonfatal ischemic stroke                                                                                                                   | 1              | (0.4%) | 1              | (0.4%) | 2     | (0.8%) |
| Nonfatal hemorrhagic stroke                                                                                                                | 0              |        | 0              |        | 0     |        |
| Note: Arterial thromboembolic events, defined according to the Antiplatelet Trialists' Collaboration classification (1994), are presented. |                |        |                |        |       |        |

Reviewer's Comment:

Applying the APTC classification to the serious adverse events, an overall trend is noted in the ranibizumab 0.5-mg dose group compared to subjects in other treatment groups. The overall frequency of such events in the ranibizumab 0.3-mg group was 6 events in 375 subjects (1.6%), 5 events in 379 subjects (1.3%) for the control groups. The overall frequency of such events in the 0.5-mg ranibizumab groups was 11 events in 379 subjects (2.9%).

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**Table 7.1.3.3-3 Intraocular Inflammation in the Study Eye during the First Treatment Year  
Studies FV2598g and FV2587g: Safety Evaluable Subjects**

| Medication     | Shim<br>Analysis | Study 25 (9/96)  |                  | Study 26 (10/96) |                  | Support<br>Group | Total<br>n |
|----------------|------------------|------------------|------------------|------------------|------------------|------------------|------------|
|                |                  | Shim<br>Analysis | Shim<br>Analysis | Shim<br>Analysis | Shim<br>Analysis |                  |            |
| <b>TOTAL</b>   | 23 (9.7%)        | 76 (10.5%)       | 34 (14.7%)       | 4 (2.8%)         | 14 (10.2%)       | 21 (15.0%)       |            |
| Isitis         | 16 (6.8%)        | 15 (6.3%)        | 15 (6.3%)        | 2 (1.4%)         | 7 (5.1%)         | 10 (7.1%)        |            |
| Vitritis       | 7 (3.0%)         | 13 (5.5%)        | 22 (9.2%)        | 2 (1.4%)         | 8 (5.8%)         | 12 (8.6%)        |            |
| Iridochoiritis | 2 (0.8%)         | 1 (0.4%)         | 2 (0.8%)         | 0                | 0                | 4 (2.9%)         |            |
| Uveitis        | 2 (0.8%)         | 0                | 1 (0.4%)         | 0                | 0                | 1 (0.7%)         |            |

**Reviewer's Comment:**

There was a dose dependent relationship between ranibizumab and intraocular inflammation in both studies.

*In Study FVZ2598g, four ranibizumab subjects had serious intraocular inflammation, two subjects in each treatment group. Two of those subjects discontinued treatment as a result. One case of serious uveitis (0.5-mg group) was treated with intravitreal antibiotics.*

In Study FVFS87, one subject in the ranibizumab 0.5 mg groups experienced a case of uveitis deemed serious. The first episode in this subject was treated with antibiotics. The second occurrence led to treatment discontinuation.

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#### 7.1.4 Other Search Strategies

No other search strategies were used to analyze adverse events.

#### 7.1.5 Common Adverse Events

##### 7.1.5.1 Eliciting adverse events data in the development program

The protocol adequately defined an adverse event. Each investigator evaluated study participants for adverse events, volunteered and elicited, at each intraocular pressure check on each study visit. An Adverse Event Form was completed to document a description of the event, onset, severity, treatment required, outcome and relatedness to the use of the study medication. Checklists were not used.

##### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The study utilized the MedDRA preferred terms for adverse event recording. The terms were sufficiently descriptive to assess adverse events expected to be experienced by the study population.

##### 7.1.5.3 Incidence of common adverse events

Table 7.1.5.3-1

Adverse Events Occurring in  $\geq 1\%$  of Patients during the First Treatment Year:  
 Pooled Safety Evaluable Subjects – Study FVF2598g and Study FVF2587g

| Adverse Event                               | Study FVF2598g | Study FVF2587g | Total       | % of Total  |
|---------------------------------------------|----------------|----------------|-------------|-------------|
| <b>Blood and Lymphatic System Disorders</b> |                |                |             |             |
| Anemia                                      | 8 (3.4%)       | 4 (2.8%)       | 11 (2.9%)   | 17 (4.5%)   |
| Thrombocytopenia                            | 0              | 0              | 3 (0.8%)    | 0           |
| <b>Cardiac Disorders</b>                    |                |                |             |             |
| Atrial fibrillation                         | 5 (2.1%)       | 3 (2.1%)       | 6 (1.6%)    | 7 (1.8%)    |
| Cardiac failure congestive                  | 4 (1.7%)       | 4 (2.8%)       | 3 (0.8%)    | 5 (1.3%)    |
| Coronary artery disease                     | 5 (2.1%)       | 0              | 3 (0.8%)    | 4 (1.1%)    |
| <b>Ear and Labyrinth Disorders</b>          |                |                |             |             |
| Vertigo                                     | 2 (0.8%)       | 5 (3.5%)       | 7 (1.9%)    | 3 (0.8%)    |
| <b>Endocrine Disorders</b>                  |                |                |             |             |
| Hypothyroidism                              | 2 (0.8%)       | 2 (1.4%)       | 3 (0.8%)    | 0           |
| <b>Eye Disorders</b>                        |                |                |             |             |
| Abnormal sensation in eye                   | 4 (1.7%)       | 0              | 6 (1.6%)    | 1 (0.3%)    |
| Altered visual depth perception             | 3 (1.3%)       | 0              | 0           | 0           |
| Anterior chamber flare                      | 6 (2.5%)       | 0              | 7 (1.9%)    | 7 (1.8%)    |
| Arcus lipoides                              | 0              | 0              | 6 (1.6%)    | 7 (1.8%)    |
| Blepharitis                                 | 14 (5.9%)      | 6 (4.2%)       | 22 (5.9%)   | 33 (8.7%)   |
| Cataract                                    | 26 (11.0%)     | 10 (7.0%)      | 37 (9.9%)   | 43 (11.3%)  |
| Choroidal neovascularization                | 27 (11.4%)     | 14 (9.8%)      | 4 (1.1%)    | 8 (2.1%)    |
| Conjunctival hemorrhage                     | 139 (58.9%)    | 65 (45.5%)     | 261 (69.6%) | 255 (67.3%) |
| Conjunctival hyperemia                      | 14 (5.9%)      | 5 (3.5%)       | 19 (5.1%)   | 22 (5.8%)   |
| Conjunctival edema                          | 3 (1.3%)       | 2 (1.4%)       | 4 (1.1%)    | 2 (0.5%)    |
| Conjunctivitis                              | 7 (3.0%)       | 0              | 7 (1.9%)    | 7 (1.8%)    |
| Conjunctivitis, allergic                    | 3 (1.3%)       | 1 (0.7%)       | 3 (0.8%)    | 9 (2.4%)    |
| Corneal abrasion                            | 7 (3.0%)       | 0              | 6 (1.6%)    | 11 (2.9%)   |

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|                                          |             |            |             |             |
|------------------------------------------|-------------|------------|-------------|-------------|
| Corneal dystrophy                        | 2 (0.8%)    | 0          | 17 (4.5%)   | 13 (3.4%)   |
| Cutis laxa                               | 1 (0.4%)    | 0          | 4 (1.1%)    | 3 (0.8%)    |
| Detachment of retinal pigment epithelium | 30 (12.7%)  | 5 (3.5%)   | 26 (6.9%)   | 22 (5.8%)   |
| Drug hypersensitivity                    | 4 (1.7%)    | 6 (4.2%)   | 1 (0.3%)    | 3 (0.8%)    |
| Dry eye                                  | 12 (5.1%)   | 12 (8.4%)  | 15 (4.0%)   | 30 (7.9%)   |
| Eye discharge                            | 14 (5.9%)   | 4 (2.8%)   | 20 (5.3%)   | 13 (3.4%)   |
| Eye hemorrhage                           | 7 (3.0%)    | 0          | 2 (0.5%)    | 3 (0.8%)    |
| Eye irritation                           | 43 (18.2%)  | 8 (5.6%)   | 40 (10.7%)  | 40 (10.6%)  |
| Eye pain                                 | 57 (24.2%)  | 24 (16.8%) | 110 (29.3%) | 105 (27.7%) |
| Eye pruritus                             | 20 (8.5%)   | 7 (4.9%)   | 28 (7.5%)   | 29 (7.7%)   |
| Eye swelling                             | 4 (1.7%)    | 2 (1.4%)   | 3 (0.8%)    | 4 (1.1%)    |
| Eyelid margin crusting                   | 1 (0.4%)    | 0          | 6 (1.6%)    | 1 (0.3%)    |
| Eyelid edema                             | 4 (1.7%)    | 2 (1.4%)   | 10 (2.7%)   | 9 (2.4%)    |
| Eyelid pain                              | 1 (0.4%)    | 0          | 3 (0.8%)    | 6 (1.6%)    |
| Eyelid ptosis                            | 3 (1.3%)    | 0          | 4 (1.1%)    | 2 (0.5%)    |
| Eyelids pruritus                         | 4 (1.7%)    | 1 (0.7%)   | 2 (0.5%)    | 2 (0.5%)    |
| Foreign body sensation in eyes           | 27 (11.4%)  | 15 (10.5%) | 49 (13.1%)  | 49 (12.9%)  |
| Glaucoma                                 | 0           | 2 (1.4%)   | 2 (0.5%)    | 2 (0.5%)    |
| Injection site hemorrhage                | 3 (1.3%)    | 3 (2.1%)   | 8 (2.1%)    | 13 (3.4%)   |
| Intraocular pressure increased           | 7 (3.0%)    | 10 (7.0%)  | 59 (15.7%)  | 61 (16.1%)  |
| Iridocyclitis                            | 0           | 0          | 0           | 4 (1.1%)    |
| Iritis                                   | 16 (6.8%)   | 2 (1.4%)   | 22 (5.9%)   | 25 (6.6%)   |
| Lacrimation increased                    | 30 (12.7%)  | 6 (4.2%)   | 41 (10.9%)  | 35 (9.2%)   |
| Macular degeneration                     | 125 (53.0%) | 89 (62.2%) | 138 (36.8%) | 136 (35.9%) |
| Macular edema                            | 20 (8.5%)   | 6 (4.2%)   | 4 (1.1%)    | 10 (2.6%)   |
| Macular scar                             | 2 (0.8%)    | 1 (0.7%)   | 6 (1.6%)    | 5 (1.3%)    |
| Maculopathy                              | 19 (8.1%)   | 5 (3.5%)   | 15 (4.0%)   | 26 (6.9%)   |
| Migraine with aura                       | 0           | 2 (1.4%)   | 0           | 0           |
| Ocular discomfort                        | 7 (3.0%)    | 1 (0.7%)   | 20 (5.3%)   | 19 (5.0%)   |
| Ocular hyperemia                         | 16 (6.8%)   | 1 (0.7%)   | 23 (6.1%)   | 26 (6.9%)   |
| Optic disc hemorrhage                    | 3 (1.3%)    | 0          | 0           | 0           |
| Optic nerve C/D ratio increased          | 0           | 2 (1.4%)   | 0           | 1 (0.3%)    |
| Photophobia                              | 6 (2.5%)    | 2 (1.4%)   | 6 (1.6%)    | 9 (2.4%)    |
| Photopsia                                | 13 (5.5%)   | 8 (5.6%)   | 14 (3.7%)   | 11 (2.9%)   |
| Posterior capsule opacification          | 7 (3.0%)    | 2 (1.4%)   | 11 (2.9%)   | 9 (2.4%)    |
| Punctate keratitis                       | 6 (2.5%)    | 2 (1.4%)   | 9 (2.4%)    | 6 (1.6%)    |
| Retinal degeneration                     | 11 (4.7%)   | 2 (1.4%)   | 21 (5.6%)   | 23 (6.1%)   |
| Retinal detachment                       | 12 (5.1%)   | 2 (1.4%)   | 15 (4.0%)   | 8 (2.1%)    |
| Retinal disorder                         | 15 (6.4%)   | 2 (1.4%)   | 28 (7.5%)   | 33 (8.7%)   |
| Retinal exudates                         | 18 (7.6%)   | 5 (3.5%)   | 20 (5.3%)   | 17 (4.5%)   |
| Retinal hemorrhage                       | 101 (42.8%) | 76 (53.1%) | 66 (17.6%)  | 66 (17.4%)  |
| Retinal edema                            | 4 (1.7%)    | 0          | 5 (1.3%)    | 1 (0.3%)    |
| Retinal pigmentation                     | 1 (0.4%)    | 0          | 5 (1.3%)    | 3 (0.8%)    |
| Retinal scar                             | 3 (1.3%)    | 3 (2.1%)   | 5 (1.3%)    | 3 (0.8%)    |
| Retinal vascular disorder                | 7 (3.0%)    | 1 (0.7%)   | 0           | 6 (1.6%)    |
| Scleral hyperemia                        | 3 (1.3%)    | 0          | 1 (0.3%)    | 1 (0.3%)    |
| Sebaceous gland disorder                 | 0           | 0          | 1 (0.3%)    | 4 (1.1%)    |
| Subretinal fibrosis                      | 24 (10.2%)  | 27 (18.9%) | 33 (8.8%)   | 28 (7.4%)   |
| Vision blurred                           | 15 (6.4%)   | 9 (6.3%)   | 27 (7.2%)   | 24 (6.3%)   |

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|                                                             |            |            |            |            |
|-------------------------------------------------------------|------------|------------|------------|------------|
| Visual acuity reduced                                       | 23 (9.7%)  | 21 (14.7%) | 25 (6.7%)  | 21 (5.5%)  |
| Visual disturbance                                          | 14 (5.9%)  | 6 (4.2%)   | 30 (8.0%)  | 30 (7.9%)  |
| Vitreous degeneration                                       | 3 (1.3%)   | 0          | 2 (0.5%)   | 0          |
| Vitreous detachment                                         | 30 (12.7%) | 26 (18.2%) | 60 (16.0%) | 59 (15.6%) |
| Vitreous disorder                                           | 0          | 0          | 4 (1.1%)   | 1 (0.3%)   |
| Vitreous floaters                                           | 14 (5.9%)  | 6 (4.2%)   | 75 (20.0%) | 78 (20.6%) |
| Vitreous hemorrhage                                         | 3 (1.3%)   | 3 (2.1%)   | 8 (2.1%)   | 8 (2.1%)   |
| Vitritis                                                    | 7 (3.0%)   | 2 (1.4%)   | 21 (5.6%)  | 34 (9.0%)  |
| <b>Gastrointestinal Disorders</b>                           |            |            |            |            |
| Abdominal discomfort                                        | 1 (0.4%)   | 0          | 1 (0.3%)   | 4 (1.1%)   |
| Abdominal pain upper                                        | 4 (1.7%)   | 2 (2.1%)   | 0          | 1 (0.3%)   |
| Colonic polyp                                               | 3 (1.3%)   | 1 (0.7%)   | 3 (0.8%)   | 4 (1.1%)   |
| Constipation                                                | 0          | 3 (2.1%)   | 4 (1.1%)   | 4 (1.1%)   |
| Diarrhea                                                    | 12 (5.1%)  | 6 (4.2%)   | 16 (4.3%)  | 9 (2.4%)   |
| Diverticulum intestinal                                     | 0          | 2 (1.4%)   | 0          | 0          |
| Dyspepsia                                                   | 7 (3.0%)   | 3 (2.1%)   | 5 (1.3%)   | 3 (0.8%)   |
| Gastroesophageal reflux disease                             | 6 (2.5%)   | 8 (5.6%)   | 10 (2.7%)  | 11 (2.9%)  |
| Hemorrhoids                                                 | 4 (1.7%)   | 1 (0.7%)   | 1 (0.3%)   | 4 (1.1%)   |
| Hiatus hernia                                               | 0          | 2 (1.4%)   | 0          | 3 (0.8%)   |
| Nausea                                                      | 10 (4.2%)  | 7 (4.9%)   | 20 (5.3%)  | 19 (5.0%)  |
| Stomach discomfort                                          | 0          | 3 (2.1%)   | 0          | 0          |
| Toothache                                                   | 4 (1.7%)   | 2 (1.4%)   | 3 (0.8%)   | 3 (0.8%)   |
| Vomiting                                                    | 2 (0.8%)   | 6 (4.2%)   | 6 (1.6%)   | 3 (0.8%)   |
| <b>General Disorders and Administration Site Conditions</b> |            |            |            |            |
| Asthenia                                                    | 4 (1.7%)   | 3 (2.1%)   | 3 (0.8%)   | 5 (1.3%)   |
| Chest pain                                                  | 7 (3.0%)   | 0          | 7 (1.9%)   | 4 (1.1%)   |
| Fatigue                                                     | 4 (1.7%)   | 2 (1.4%)   | 6 (1.6%)   | 4 (1.1%)   |
| Edema peripheral                                            | 9 (3.8%)   | 0          | 9 (2.4%)   | 7 (1.8%)   |
| Pain                                                        | 2 (0.8%)   | 0          | 4 (1.1%)   | 3 (0.8%)   |
| Pyrexia                                                     | 2 (0.8%)   | 2 (1.4%)   | 9 (2.4%)   | 5 (1.3%)   |
| <b>Immune System Disorders</b>                              |            |            |            |            |
| Drug hypersensitivity                                       | 3 (1.3%)   | 1 (0.7%)   | 4 (1.1%)   | 5 (1.3%)   |
| Hypersensitivity                                            | 1 (0.4%)   | 3 (2.1%)   | 6 (1.6%)   | 6 (1.6%)   |
| Seasonal allergy                                            | 2 (0.8%)   | 6 (4.2%)   | 7 (1.9%)   | 7 (1.8%)   |
| <b>Infections and Infestations</b>                          |            |            |            |            |
| Bronchitis                                                  | 12 (5.1%)  | 9 (6.3%)   | 20 (5.3%)  | 23 (6.1%)  |
| Bronchitis, chronic                                         | 0          | 2 (1.4%)   | 0          | 0          |
| Cellulitis                                                  | 3 (1.3%)   | 0          | 5 (1.3%)   | 3 (0.8%)   |
| Cystitis                                                    | 1 (0.4%)   | 2 (1.4%)   | 6 (1.6%)   | 8 (2.1%)   |
| Diverticulitis                                              | 2 (0.8%)   | 0          | 7 (1.9%)   | 7 (1.8%)   |
| Ear infection                                               | 2 (0.8%)   | 3 (2.1%)   | 4 (1.1%)   | 4 (1.1%)   |
| Fungal infection                                            | 1 (0.4%)   | 0          | 1 (0.3%)   | 4 (1.1%)   |
| Gastroenteritis, viral                                      | 5 (2.1%)   | 0          | 6 (1.6%)   | 11 (2.9%)  |
| Herpes zoster                                               | 3 (1.3%)   | 0          | 10 (2.7%)  | 5 (1.3%)   |
| Influenza                                                   | 6 (2.5%)   | 1 (0.7%)   | 13 (3.5%)  | 14 (3.7%)  |
| Kidney infection                                            | 4 (1.7%)   | 0          | 3 (0.8%)   | 2 (0.5%)   |
| Localised infection                                         | 5 (2.1%)   | 0          | 3 (0.8%)   | 4 (1.1%)   |
| Nasopharyngitis                                             | 23 (9.7%)  | 15 (10.3%) | 42 (11.2%) | 22 (5.8%)  |
| Pneumonia                                                   | 10 (4.2%)  | 5 (3.5%)   | 15 (4.0%)  | 13 (3.4%)  |

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|                                                                               |           |           |           |           |
|-------------------------------------------------------------------------------|-----------|-----------|-----------|-----------|
| Sinusitis                                                                     | 9 (3.8%)  | 9 (6.3%)  | 20 (5.3%) | 21 (5.5%) |
| Skin infection                                                                | 3 (1.3%)  | 0         | 0         | 1 (0.3%)  |
| Tooth abscess                                                                 | 3 (1.3%)  | 0         | 2 (0.5%)  | 2 (0.5%)  |
| Tooth infection                                                               | 0         | 0         | 4 (1.1%)  | 3 (0.8%)  |
| Upper respiratory tract infection                                             | 15 (6.4%) | 6 (4.2%)  | 23 (6.1%) | 19 (5.0%) |
| Urinary tract infection                                                       | 12 (5.1%) | 9 (6.3%)  | 21 (5.8%) | 18 (4.7%) |
| <b>Injury, Poisoning and Procedural Complications Contrast Media Reaction</b> |           |           |           |           |
| Contusion                                                                     | 6 (2.5%)  | 5 (3.5%)  | 8 (2.1%)  | 7 (1.8%)  |
| Excoriation                                                                   | 2 (0.8%)  | 1 (0.7%)  | 5 (1.3%)  | 5 (1.3%)  |
| Fall                                                                          | 5 (2.1%)  | 1 (0.7%)  | 7 (1.9%)  | 8 (2.1%)  |
| Hip fracture                                                                  | 0         | 0         | 4 (1.1%)  | 1 (0.3%)  |
| Muscle strain                                                                 | 6 (2.5%)  | 0         | 4 (1.1%)  | 1 (0.3%)  |
| Post procedural pain                                                          | 3 (1.3%)  | 1 (0.7%)  | 1 (0.3%)  | 2 (0.5%)  |
| Skin laceration                                                               | 3 (1.3%)  | 2 (1.4%)  | 9 (2.4%)  | 4 (1.1%)  |
| Tooth injury                                                                  | 0         | 2 (1.4%)  | 2 (0.5%)  | 0         |
| Wrist fracture                                                                | 3 (1.3%)  | 0         | 5 (1.3%)  | 2 (0.5%)  |
| <b>Investigations</b>                                                         |           |           |           |           |
| Blood cholesterol increased                                                   | 4 (1.7%)  | 2 (1.4%)  | 2 (0.5%)  | 7 (1.8%)  |
| Blood glucose increased                                                       | 4 (1.7%)  | 3 (2.1%)  | 9 (2.4%)  | 8 (2.1%)  |
| Blood pressure increased                                                      | 14 (5.9%) | 3 (2.1%)  | 18 (4.8%) | 17 (4.5%) |
| Heart rate irregular                                                          | 0         | 2 (1.4%)  | 1 (0.3%)  | 0         |
| Prostate specific antigen increased                                           | 2 (0.8%)  | 2 (1.4%)  | 4 (1.1%)  | 4 (1.1%)  |
| Weight decreased                                                              | 3 (1.3%)  | 2 (1.4%)  | 2 (0.5%)  | 0         |
| <b>Metabolism and Nutrition Disorders</b>                                     |           |           |           |           |
| Dehydration                                                                   | 0         | 2 (1.4%)  | 3 (0.8%)  | 1 (0.3%)  |
| Diabetes mellitus                                                             | 0         | 1 (0.7%)  | 4 (1.1%)  | 9 (2.4%)  |
| Gout                                                                          | 3 (1.3%)  | 1 (0.7%)  | 4 (1.1%)  | 8 (2.1%)  |
| Hypercholesterolemia                                                          | 5 (2.1%)  | 4 (2.8%)  | 7 (1.9%)  | 9 (2.4%)  |
| Hyperlipidemia                                                                | 1 (0.4%)  | 2 (1.4%)  | 4 (1.1%)  | 5 (1.3%)  |
| Hypokalemia                                                                   | 4 (1.7%)  | 3 (2.1%)  | 7 (1.9%)  | 2 (0.5%)  |
| <b>Musculoskeletal and Connective Tissue Disorders</b>                        |           |           |           |           |
| Arthralgia                                                                    | 14 (5.9%) | 9 (6.3%)  | 19 (5.1%) | 18 (4.7%) |
| Arthritis                                                                     | 14 (5.9%) | 5 (3.5%)  | 9 (2.4%)  | 12 (3.2%) |
| Back pain                                                                     | 13 (5.5%) | 13 (9.1%) | 22 (5.9%) | 15 (4.0%) |
| Bone pain                                                                     | 0         | 3 (2.1%)  | 0         | 0         |
| Bursitis                                                                      | 6 (2.5%)  | 0         | 1 (0.3%)  | 1 (0.3%)  |
| Exostosis                                                                     | 0         | 2 (1.4%)  | 0         | 1 (0.3%)  |
| Joint swelling                                                                | 4 (1.7%)  | 0         | 3 (0.8%)  | 1 (0.3%)  |
| Muscle spasms                                                                 | 3 (1.3%)  | 3 (2.1%)  | 6 (1.6%)  | 5 (1.3%)  |
| Myalgia                                                                       | 0         | 2 (1.4%)  | 0         | 0         |
| Neck pain                                                                     | 1 (0.4%)  | 0         | 4 (1.1%)  | 5 (1.3%)  |
| Osteoarthritis                                                                | 5 (2.1%)  | 0         | 4 (1.1%)  | 1 (0.3%)  |
| Osteoporosis                                                                  | 0         | 5 (3.5%)  | 1 (0.3%)  | 4 (1.1%)  |
| Pain in extremity                                                             | 7 (3.0%)  | 4 (2.8%)  | 13 (3.5%) | 10 (2.6%) |
| Rotator cuff syndrome                                                         | 3 (1.3%)  | 0         | 0         | 3 (0.8%)  |
| Shoulder pain                                                                 | 7 (3.0%)  | 1 (0.7%)  | 6 (1.6%)  | 4 (1.1%)  |
| <b>Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)</b>   |           |           |           |           |
| Basal cell carcinoma                                                          | 8 (3.4%)  | 2 (1.4%)  | 10 (2.7%) | 6 (1.6%)  |
| Schorrheic keratosis                                                          | 0         | 2 (1.4%)  | 1 (0.3%)  | 1 (0.3%)  |

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|                                                        |           |           |           |           |
|--------------------------------------------------------|-----------|-----------|-----------|-----------|
| Skin cancer                                            | 1 (0.4%)  | 0         | 4 (1.1%)  | 3 (0.8%)  |
| Skin papilloma                                         | 0         | 2 (1.4%)  | 1 (0.3%)  | 1 (0.3%)  |
| <b>Nervous System Disorders</b>                        |           |           |           |           |
| Dizziness                                              | 16 (6.8%) | 4 (2.8%)  | 14 (3.7%) | 12 (3.2%) |
| Headache                                               | 15 (6.4%) | 7 (4.9%)  | 35 (9.3%) | 25 (6.6%) |
| Syncope                                                | 4 (1.7%)  | 3 (2.1%)  | 2 (0.5%)  | 6 (1.6%)  |
| Transient ischemic attack                              | 0         | 2 (1.4%)  | 0         | 2 (0.5%)  |
| <b>Psychiatric Disorders</b>                           |           |           |           |           |
| Anxiety                                                | 1 (0.4%)  | 8 (5.6%)  | 11 (2.9%) | 11 (2.9%) |
| Depression                                             | 8 (3.4%)  | 7 (4.9%)  | 9 (2.4%)  | 12 (3.2%) |
| Insomnia                                               | 7 (3.0%)  | 2 (1.4%)  | 8 (2.1%)  | 14 (3.7%) |
| <b>Renal and Urinary Disorders</b>                     |           |           |           |           |
| Nephrolithiasis                                        | 0         | 3 (2.1%)  | 3 (0.8%)  | 0         |
| Renal cyst                                             | 0         | 3 (2.1%)  | 1 (0.3%)  | 0         |
| <b>Reproductive System and Breast Disorders</b>        |           |           |           |           |
| Benign prostatic hyperplasia                           | 1 (0.4%)  | 2 (1.4%)  | 3 (0.8%)  | 8 (2.1%)  |
| Prostatitis                                            | 0         | 2 (1.4%)  | 0         | 1 (0.3%)  |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b> |           |           |           |           |
| Asthma                                                 | 2 (0.8%)  | 3 (2.1%)  | 8 (2.1%)  | 7 (1.8%)  |
| Chronic obstructive airways disease, exacerbated       | 1 (0.4%)  | 2 (1.4%)  | 0         | 11 (2.9%) |
| Chronic obstructive pulmonary disease                  | 0         | 1 (0.7%)  | 3 (0.8%)  | 4 (1.1%)  |
| Cough                                                  | 10 (4.2%) | 8 (5.6%)  | 32 (8.5%) | 20 (5.3%) |
| Dyspnea                                                | 3 (1.3%)  | 4 (2.8%)  | 10 (2.7%) | 8 (2.1%)  |
| Emphysema                                              | 0         | 3 (2.1%)  | 1 (0.3%)  | 2 (0.5%)  |
| Epistaxis                                              | 0         | 2 (1.4%)  | 2 (0.5%)  | 1 (0.3%)  |
| Hypoxia                                                | 3 (1.3%)  | 0         | 2 (0.5%)  | 0         |
| Pharyngolaryngeal pain                                 | 1 (0.4%)  | 4 (2.8%)  | 3 (0.8%)  | 3 (0.8%)  |
| Rhinitis allergic                                      | 0         | 2 (1.4%)  | 0         | 0         |
| Rhinorrhea                                             | 3 (1.3%)  | 1 (0.7%)  | 7 (1.9%)  | 4 (1.1%)  |
| Sinus congestion                                       | 3 (1.3%)  | 0         | 5 (1.3%)  | 2 (0.5%)  |
| <b>Skin and Subcutaneous Disorders</b>                 |           |           |           |           |
| Actinic keratosis                                      | 6 (2.5%)  | 1 (0.7%)  | 4 (1.1%)  | 1 (0.3%)  |
| Decubitus ulcer                                        | 0         | 2 (1.4%)  | 0         | 0         |
| Pruritus                                               | 2 (0.8%)  | 1 (0.7%)  | 4 (1.1%)  | 8 (2.1%)  |
| Rash                                                   | 9 (3.8%)  | 4 (2.8%)  | 9 (2.4%)  | 8 (2.1%)  |
| <b>Surgical and Medical Procedures</b>                 |           |           |           |           |
| Nasal sinus drainage                                   | 0         | 0         | 0         | 5 (1.3%)  |
| <b>Vascular Disorders</b>                              |           |           |           |           |
| Hypertension                                           | 23 (9.7%) | 12 (8.4%) | 23 (6.1%) | 29 (7.7%) |
| Hypotension                                            | 4 (1.7%)  | 3 (2.1%)  | 3 (0.8%)  | 0         |
| Orthostatic hypotension                                | 0         | 2 (1.4%)  | 0         | 0         |

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.

#### Reviewer's Comment:

The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus either control are highlighted.

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Adverse events which occurred most frequently (i.e.  $\geq 10\%$ ) in the study eye of the ranibizumab treatment groups were conjunctival hemorrhage, eye pain, increased IOP, retinal disorder, and vitreous floaters. Many of these adverse events are commonly associated with conjunctival anesthetic and intravitreal injection procedures.

Elevated intraocular pressure was seen in a higher percentage of subjects in the ranibizumab groups than the sham-injection group. The ranibizumab subjects were also found to use ocular hypotensive and antihypertensive agents more frequently. This trend with the use of antihypertensive agents was noted at screening as well.

Intraocular inflammation including the Med DRA preferred terms iritis, iridocyclitis, vitritis, uveitis and anterior chamber inflammation was experienced at an increased rate in ranibizumab treated subjects in both studies. In study FVF2598g, 60 of 477 subjects (12.5%) and in study FVF2587g 35 of 277 subjects (12.6%) in the ranibizumab groups experienced intraocular inflammation in the study eye. Findings from the objective slit lamp examination were consistent with occurrence of intraocular inflammation adverse events and are discussed

Table 7.1.5.3-2 Ocular Adverse Events in the Fellow Eye during the First Treatment Year  
Occurring in  $\geq 5\%$  of Patients:  
Safety Evaluable Population

| MedDRA System<br>Preferred Term | Study 1<br>FVF2598g<br>n=477 | Study 2<br>FVF2587g<br>n=277 | Ranibizumab Pooled<br>n=754 | Sham Pooled<br>n=377 |
|---------------------------------|------------------------------|------------------------------|-----------------------------|----------------------|
| Total *                         | 168 (71.2%)                  | 188 (72.7%)                  | 258 (68.8%)                 | 265 (69.9%)          |
| Macular degeneration            | 60 (25.4%)                   | 32 (22.4%)                   | 91 (24.3%)                  | 83 (21.9%)           |
| Retinal hemorrhage              | 47 (19.9%)                   | 26 (18.2%)                   | 68 (18.1%)                  | 71 (18.7%)           |
| Vitreous detachment             | 31 (13.1%)                   | 17 (11.9%)                   | 43 (11.5%)                  | 39 (10.3%)           |
| Blepharitis                     | 16 (6.8%)                    | 6 (4.2%)                     | 25 (6.6%)                   | 29 (7.7%)            |
| Cataract                        | 10 (4.2%)                    | 5 (3.5%)                     | 16 (4.3%)                   | 19 (5.0%)            |
| Choroidal neovascularization    | 11 (4.7%)                    | 6 (4.2%)                     | 28 (7.5%)                   | 29 (7.7%)            |
| Dry Eye                         | 13 (5.5%)                    | 12 (8.4%)                    | 12 (3.2%)                   | 19 (5.0%)            |
| Retinal disorder                | 11 (4.7%)                    | 2 (1.4%)                     | 17 (4.5%)                   | 21 (5.5%)            |
| Visual acuity reduced           | 18 (7.6%)                    | 9 (6.3%)                     | 13 (3.5%)                   | 15 (4.0%)            |

**Reviewer's Comment:**

Ocular adverse events seen in the fellow eye during the first treatment year are those expected in this patient population.

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7.1.5.4 Common adverse event tables  
Refer to Section 7.1.5.3 Incidence of Common Adverse Events

7.1.5.5 Identifying common and drug-related adverse events

**Reviewer's Comment:**

*Intraocular inflammation which includes Med DRA preferred terms iritis, iridocyclitis, vitritis, uveitis and anterior chamber inflammation was noted to occur in a dose dependent manner in the ranibizumab treated subjects in both studies. In study FVF2598g, 60 of 477 subjects (12.5%) and in study FVF2587g 35 of 277 subjects (12.6%) in the ranibizumab groups experienced intraocular inflammation in the study eye. Findings from the objective slit lamp examination were consistent with occurrence of intraocular inflammation adverse events.*

*Refer to Table 7.1.3.3-3 Intraocular Inflammation in the Study Eye during the First Treatment Year Studies FVF2598g and FVF2587g: Safety Evaluable Subjects for details.*

7.1.5.6 Additional analyses and explorations  
Not applicable. There were no additional analyses or explorations performed regarding adverse events.

**7.1.6 Less Common Adverse Events**

The overall safety population was not sufficiently large to identify rare events of significant concern.

**7.1.7 Laboratory Findings**

During clinical trials FVF2587g and FVF2598g, laboratory assessments were to be performed on all of the subjects at the Screening Visit and Month 12 or Early Termination Visit.

**Reviewer's Comment:**

*None of the laboratory abnormalities noted were serious adverse events, led to treatment or study discontinuation.*

**7.1.7.1 Overview of laboratory testing in the development program**

Laboratory testing during the development program was performed to determine systemic ranibizumab concentrations, immunoreactivity to ranibizumab and if any significant changes in blood chemistry, hematology or coagulation measures could be found.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values  
Such analyses were not performed. Laboratory investigations were limited by the low to non-detectable ranibizumab concentrations after intravitreal injection.

**7.1.7.3 Standard analyses and explorations of laboratory data**

The analyses of laboratory data consisted of description of the findings.

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#### 7.1.7.4 Additional analyses and explorations

No additional analyses and explorations were performed.

#### 7.1.7.5 Special assessments

Laboratory abnormality adverse events were reported in less than 2% of subjects. None of the laboratory abnormalities were serious adverse events, led to treatment or study discontinuation or were considered by the investigators as study drug related.

#### 7.1.8 Vital Signs

Vital signs were measured at the Screening Visit and at each monthly visit post treatment. Overall, on average, both ranibizumab-treated and sham-treated subjects showed little change from baseline in vital signs throughout the first treatment year. There were no meaningful differences in the mean change from baseline in the temperature, pulse rate and respiration rate.

Regarding blood pressure, at Month 12, the mean changes from baseline were -1.6, -0.6, and -4.4 mmHg in systolic pressure and -2.0, -1.7, and -0.5 mm Hg in diastolic pressure for the sham, 0.3-mg, and 0.5-mg groups, respectively.

Some subjects had adverse events of increased blood pressure, worsening of preexisting hypertension, or newly diagnosed hypertension during the first treatment year. There was no imbalance among treatment groups in the proportion of subjects with such adverse events (15.7% in the sham group, 13.4% in the 0.3-mg group, and 12.6% in the 0.5-mg group.)

#### 7.1.8.1 Overview of vital signs testing in the development program

Refer to Section 7.1.1.

#### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

These analyses were not performed.

#### 7.1.8.3 Standard analyses and explorations of vital signs data

These analyses were not performed.

#### 7.1.8.4 Additional analyses and explorations

Additional analyses and explorations of vital signs data were not performed.

#### 7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not obtained during the development program for this product.

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#### 7.1.10 Immunogenicity

Serum samples for the evaluation of immunoreactivity to ranibizumab were obtained from subjects at screening and prior to study drug administration at Months 6 and 12. The assay demonstrated immunoreactivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies.

There was no imbalance between ranibizumab-treated and sham-treated subjects regarding immunoreactivity to ranibizumab. The assay indicated positivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies. All three treatment groups had similar increases in positivity during the treatment period.

Table 7.1.10-1 Immunoreactivity to Ranibizumab in the First Treatment Year

|           | Screening        | Month 6          | Month 12          | Month 18        | Month 24         | Month 30          |
|-----------|------------------|------------------|-------------------|-----------------|------------------|-------------------|
| Screening | 5/215<br>(2.3%)  | 6/215<br>(2.8%)  | 7/218<br>(3.2%)   | 8/131<br>(6.1%) | 12/125<br>(9.6%) | 7/123<br>(5.7%)   |
| Month 6   | 19/201<br>(9.5%) | 15/211<br>(7.1%) | 17/207<br>(8.2%)  | 6/114<br>(5.3%) | 11/120<br>(9.2%) | 10/116<br>(8.6%)  |
| Month 12  | 20/206<br>(9.7%) | 22/222<br>(9.9%) | 26/219<br>(11.9%) | 7/125<br>(5.6%) | 9/123<br>(7.3%)  | 16/129<br>(12.4%) |

Note: Table entries are numbers of subjects with positive immunoreactivity over numbers of subjects with evaluable samples. LTR=0.7 log titer.

Exploratory subgroup analyses based on immunoreactivity to ranibizumab were performed to determine whether the appearance of immunoreactivity was related to key safety and efficacy outcomes. The analysis population was divided into three subgroups: subjects who had a negative or missing test result at screening and negative post-baseline results, subjects who had a negative or missing test result at screening but at least one positive post-baseline result, and subjects who had a positive test result at screening. Visual acuity outcomes and the occurrence of intraocular inflammation and autoimmune adverse events were examined by treatment group for each immunoreactivity subgroup. No clinically relevant differences between immunoreactivity subgroups were identified in study FVF2598g.

In Study FVF2587g, with regard to intraocular inflammation adverse events, proportionately more ranibizumab-treated subjects who were immunoreactive at some time point experienced intraocular inflammation events than subjects who were never immunoreactive. Twenty-eight percent (5 of 18) of ranibizumab-treated subjects who were immunoreactive during treatment only and thirty-two percent of subjects (6 of 19) who were immunoreactive at baseline experienced inflammation adverse events in the study eye, compared with 10% of ranibizumab-treated subjects (23 of 230) who were never immunoreactive. Of the 12 verteporfin PDT-treated subjects who were immunoreactive at some time point, none experienced an intraocular inflammation adverse event.

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Table 7.1.10-2 Intracocular Inflammation in Subjects with Immunoreactivity  
 Based on the Initial and Confirmatory Assays (ECLAS 4.FBV.8 and 4.FBV.10)  
 Studies FVF2428g, FVF2587g, FVF3192g (First Treatment Year) and FVF2598g (2-Year Treatment Period)  
 Safety Evaluable Subjects

| Study ID / Visit      | Study Day / Visit                    | Any<br>Intraocular<br>Inflammation | Any<br>Intraocular<br>Inflammation | Screen Month 1 | Screen Month 4                    |
|-----------------------|--------------------------------------|------------------------------------|------------------------------------|----------------|-----------------------------------|
|                       |                                      |                                    |                                    |                |                                   |
| FVF2428g <sup>1</sup> | Verteporfin PDT + Sham               | 91103                              | 34 / Month 1                       | 1,200          | Month 4                           |
|                       | Verteporfin PDT + Ranibizumab 0.5 mg | 91308                              | -7 / Screening                     | 0.884          | No                                |
|                       |                                      |                                    | 366 / Month 12                     | 0.767          |                                   |
|                       | Verteporfin PDT                      | 319001                             | 386 / Month 12                     | 0.797          | No                                |
|                       |                                      | 334008                             | -12 / Screening                    | 1.130          | No                                |
|                       |                                      |                                    | 190 / Month 6                      | 0.902          | No                                |
|                       |                                      | 401002                             | -8 / Screening                     | 1.820          | No                                |
|                       |                                      |                                    | 186 / Month 6                      | 1.780          |                                   |
|                       | Ranibizumab 0.3mg                    | 321003                             | 361 / Month 12                     | 1.800          |                                   |
|                       |                                      |                                    | -7 / Screening                     | 0.945          | Yes - Vitritis Screen Month 1     |
|                       |                                      | 334003                             | 176 / Month 6                      | 2.300          | Yes - Vitritis Month 4            |
|                       |                                      | 337012                             | -26 / Screening                    | 0.938          | Yes - Vitritis Month 5            |
|                       |                                      | 351004                             | 344 / Month 12                     | 2.190          | No                                |
| FVF2587g              |                                      | 352006                             | -10 / Screening                    | 2.070          | No                                |
|                       |                                      |                                    | 180 / Month 6                      | 1.890          | No                                |
|                       |                                      |                                    | 362 / Month 12                     | 1.860          | No                                |
|                       |                                      | 403003                             | -1 / Screening                     | 0.910          | No                                |
|                       |                                      | 306020                             | 174 / Month 6                      | 1.530          | Yes - Vitritis Months 1 and 2     |
|                       | Ranibizumab 0.5mg                    |                                    | 362 / Month 12                     | 1.850          |                                   |
|                       |                                      | 337009                             | 364 / Month 12                     | 1.270          | No                                |
|                       |                                      | 342007                             | 174 / Month 6                      | 2.450          | Yes - Vitritis, Vitritis Month 11 |
|                       |                                      |                                    | 360 / Month 12                     | 3.060          |                                   |
|                       |                                      | 346001                             | 182 / Month 6                      | 1.260          | No                                |

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| Study ID | Treatment Group   | Study Day / Visit of<br>Positive<br>Intravitreal<br>Assay | Intravitreal<br>Assay Log Titer | Any<br>Intraocular<br>Inflammation<br>Diagnosis | Study Visit of<br>Intraocular<br>Inflammation<br>Diagnosis |
|----------|-------------------|-----------------------------------------------------------|---------------------------------|-------------------------------------------------|------------------------------------------------------------|
| 399001   | Sham              | 36 / Month 12                                             | 1.70                            |                                                 |                                                            |
|          |                   | -28 / Screening                                           | 1.240                           |                                                 | Month 7                                                    |
|          |                   | 182 / Month 6                                             | 0.993                           | Yes - Uveitis <sup>3</sup>                      |                                                            |
| 102004   |                   | 365 / Month 12                                            | 0.932                           |                                                 |                                                            |
|          |                   | 183 / Month 6                                             | 1.230                           | No                                              |                                                            |
|          |                   | 358 / Month 12                                            | 2.090                           |                                                 |                                                            |
|          |                   | 463 / Early term                                          | 2.060                           |                                                 |                                                            |
| 116002   |                   | 723 / Month 24                                            | 2.560                           | No                                              |                                                            |
| 139004   |                   | -28 / Screening                                           | 2.100                           | Yes - Iritis                                    | Day 7                                                      |
|          |                   | 176 / Month 6                                             | 2.060                           |                                                 |                                                            |
|          | Ranibizumab 0.3mg | 358 / Month 12                                            | 2.170                           |                                                 |                                                            |
|          |                   | 729 / Month 24                                            | 2.340                           |                                                 |                                                            |
| 150003   |                   | 181 / Month 6                                             | 0.864                           | No                                              |                                                            |
|          |                   | 393 / Month 12                                            | 0.863                           |                                                 |                                                            |
| 182003   |                   | 355 / Month 12                                            | 0.903                           | No                                              |                                                            |
|          |                   | 361 / Month 12                                            | 1.850                           | No                                              |                                                            |
| 101021   |                   | 719 / Month 24                                            | 1.810                           |                                                 |                                                            |
| 110004   |                   | 728 / Month 24                                            | 1.490                           | No                                              |                                                            |
| 112002   |                   | 716 / Month 24                                            | 0.866                           | No                                              |                                                            |
| 125007   |                   | 183 / Month 6                                             | 0.918                           | No                                              |                                                            |
| 141009   |                   | 721 / Month 24                                            | 1.270                           | No                                              |                                                            |
| 143001   |                   | -13 / Screening                                           | 3.350                           | Iritis                                          | Month 2                                                    |
|          |                   | 177 / Month 6                                             | 3.740                           |                                                 |                                                            |
| 146001   |                   | 714 / Month 24                                            | 1.080                           | No                                              |                                                            |
| 149006   |                   | 364 / Month 12                                            | 3.150                           | Iritis                                          | Month 15 <sup>4</sup>                                      |
|          |                   | 717 / Month 24                                            | 2.120                           |                                                 |                                                            |
| 159013   |                   | 360 / Month 12                                            | 2.000                           | No                                              |                                                            |
|          |                   | 724 / Month 24                                            | 1.890                           |                                                 |                                                            |
| 165002   |                   | -21 / Screening                                           | 0.910                           | No                                              |                                                            |
|          |                   | 175 / Month 6                                             | 0.993                           |                                                 |                                                            |
|          |                   | 368 / Month 24                                            | 0.793                           |                                                 |                                                            |

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| Study    | Treatment Group    | Subject ID | Study Day/Veterinarian<br>Positive<br>Intracocular<br>Inflammation | Assay Log Filter | Any<br>Intracocular<br>Inflammation<br>Diagnosed | Study Visit<br>Intracocular<br>Inflammation<br>Diagnosed |
|----------|--------------------|------------|--------------------------------------------------------------------|------------------|--------------------------------------------------|----------------------------------------------------------|
| FVF3192g | Ranibizumab 0.5 mg | 170010     | 365 / Month 12                                                     | 2.770            | No                                               |                                                          |
|          |                    | 177006     | 715 / Month 24                                                     | 2.890            |                                                  | Day 7                                                    |
|          |                    |            | 358 / Month 12                                                     | 1.870            | Iritis                                           |                                                          |
|          |                    |            | 717 / Month 24                                                     | 1.850            |                                                  |                                                          |
|          |                    | 102001     | 722 / Month 24                                                     | 0.922            | No                                               |                                                          |
|          |                    | 104002     | 719 / Month 24                                                     | 1.140            | No                                               |                                                          |
|          |                    | 106002     | 722 / Month 24                                                     | 1.130            | No                                               |                                                          |
|          |                    | 122002     | 359 / Month 12                                                     | 1.630            | No                                               |                                                          |
|          |                    |            | 723 / Month 24                                                     | 1.770            |                                                  |                                                          |
|          |                    | 124003     | 722 / Month 24                                                     | 0.782            | No                                               |                                                          |
|          |                    | 126001     | 174 / Month 6                                                      | 1.700            | No                                               |                                                          |
|          |                    |            | 357 / Month 12                                                     | 2.040            |                                                  |                                                          |
|          |                    |            | 727 / Month 24                                                     | 1.480            |                                                  |                                                          |
|          |                    | 141008     | 181 / Month 6                                                      | 1.570            | No                                               |                                                          |
|          |                    |            | 362 / Month 12                                                     | 1.940            |                                                  |                                                          |
|          |                    |            | 726 / Month 24                                                     | 2.340            |                                                  |                                                          |
|          |                    | 141013     | 715 / Month 24                                                     | 2.610            | Vitritis                                         | Day 0                                                    |
|          |                    | 143010     | 722 / Month 24                                                     | 2.440            | No                                               |                                                          |
|          |                    | 152004     | 522 / Early Term                                                   | 0.752            | No                                               |                                                          |
|          |                    | 153006     | 183 / Month 6                                                      | 1.900            | No                                               |                                                          |
|          |                    |            | 365 / Month 12                                                     | 1.530            |                                                  |                                                          |
| FVF3192g | Sham               |            | 718 / Month 24                                                     | 2.070            |                                                  |                                                          |
|          | Ranibizumab 0.5 mg | 159017     | 716 / Month 24                                                     | 0.780            | No                                               |                                                          |
|          |                    | 167002     | 717 / Month 24                                                     | 1.230            | No                                               |                                                          |
|          |                    | 188005     | 717 / Month 24                                                     | 1.250            | No                                               |                                                          |
|          |                    | 534001     | -7 / Screening                                                     | 2.520            | Vitritis                                         | Month 1                                                  |
|          |                    | 507018     | 357 / Month 12                                                     | 0.875            | No                                               |                                                          |
|          |                    | 522002     | 367 / Month 12                                                     | 1.530            | No                                               |                                                          |

1 In Study FVF2438g, intravitreal injections (sham or ranibizumab 0.5 mg) were given every month and verapamil PDT every 3 months.  
2 Iritis diagnosed 1 day after Month 4 injection.

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3 Intra diagnosed day of injection. Injection was not held.  
4 No resolution of uveitis noted in CRFs submitted.  
5 Uveitis diagnosed 3 days post Month 7 injection. Serious AE led to treatment discontinuation in Month 9.  
6 Treatment discontinued.

Reviewer's Comment:  
*Fifty subjects in Studies FVF2428g, FVF2587g and FVF2598g had measurable immunoreactivity based upon initial and confirmatory assays. Thirteen of these subjects experienced episodes of intraocular inflammation.*  
*In subjects with an immunoreactivity assay log titer of > 2.00, 31% experienced at least one episode of intraocular inflammation.*  
*In subjects with an immunoreactivity assay log titer of > 3.00, 100% experienced an episode of intraocular inflammation.*

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#### 7.1.11 Human Carcinogenicity

Not applicable.

#### 7.1.12 Special Safety Studies

Safety analysis was based on an evaluation of other safety parameters, as well, which included visual acuity (best corrected), intraocular pressure, ocular signs by slit lamp examination and indirect ophthalmoscopy the results of which are included throughout the safety review.

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This is not a therapeutic class with known abuse potential or apparent withdrawal potential.

#### 7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. There was no inadvertent exposure to the product in pregnant women during the development program.

#### 7.1.15 Assessment of Effect on Growth

The intended population for this product is adults with age-related macular degeneration, a disease that does not exist in the pediatric age group. This application contains no pediatric data.

#### 7.1.16 Overdose Experience

This product has no overdose potential and no studies were performed.

#### 7.1.17 Postmarketing Experience

This product has not yet been marketed.

### 7.2 Adequacy of Patient Exposure and Safety Assessments

The safety and exposure database for Ranibizumab included in this application is derived from 976 ranibizumab-treated subjects with neovascular age-related macular degeneration, in six clinical trials.

#### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The submitted clinical study reports and clinical protocols related to the development program of ranibizumab were analyzed in this review. Proposed draft labeling and Case Report Forms for discontinued subjects in studies FVF2587g and FVF2598g were provided and reviewed. Refer to Section 4.1.

##### 7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 for the table of clinical studies.

##### 7.2.1.2 Demographics

Refer to Table 6.1.3.1-9 and Table 6.1.3.2-9 Demographic Statistics by Treatment Group for Studies FVF2598g and FVF2587g.

#### Reviewer's Comments:

*There are no remarkable differences between treatment groups in baseline demographic characteristics.*

*Subgroup analyses did not reveal any differences in the studies' success on the primary efficacy endpoint.*

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## 7.2.1.3 Extent of exposure (dose/duration)

Table 7.2.1.3-1 Extent of Exposure to Study Drug or Sham Injection  
 Safety Evaluable Subjects

|                                        | Verteporfin PDT | Sham PDT     | Verteporfin PDT | Sham PDT     | Verteporfin PDT | Sham PDT     |
|----------------------------------------|-----------------|--------------|-----------------|--------------|-----------------|--------------|
| Number of injections <sup>a</sup>      |                 |              |                 |              |                 |              |
| Mean (SD)                              | 11.7 (2.7)      | 12.4 (1.9)   | 12.3 (2.2)      | 12.0 (2.5)   | 12.2 (2.1)      | 12.1 (2.2)   |
| Frequency                              |                 |              |                 |              |                 |              |
| < 10                                   | 27 (11.4%)      | 10 (4.2%)    | 15 (6.3%)       | 17 (11.9%)   | 9 (6.6%)        | 13 (9.3%)    |
| 10-12                                  | 55 (23.3%)      | 36 (15.1%)   | 40 (16.7%)      | 21 (14.7%)   | 29 (21.2%)      | 29 (20.7%)   |
| 13                                     | 154 (65.3%)     | 192 (80.7%)  | 184 (77.0%)     | 105 (73.4%)  | 99 (72.3%)      | 98 (70.0%)   |
| Treatment duration (days) <sup>b</sup> |                 |              |                 |              |                 |              |
| Mean (SD)                              | 332.7 (80.0)    | 350.6 (54.7) | 346.2 (61.5)    | 337.1 (75.0) | 346.2 (61.8)    | 345.6 (59.7) |

<sup>a</sup> Of 13 scheduled injections from Day 0 to Month 12 visits. The verteporfin PDT group received sham injections.

<sup>b</sup> The number of days between the first and the last injection on or prior to Month 12 visit.

## Reviewer's Comment:

The extent of exposure was similar between all treatment groups in each study. The vast majority of subjects received 10 or more treatment injections. The mean treatment duration ranged from 332.7 days to 350.6 days among the treatment groups.

Table 7.2.1.3-2  
 Extent of Exposure to Study Treatment with Verteporfin or Sham PDT  
 Safety Evaluable Subjects in the First Treatment Year

|                                        | Verteporfin PDT | Sham PDT     | Verteporfin PDT | Sham PDT |
|----------------------------------------|-----------------|--------------|-----------------|----------|
| Number of Treatments                   |                 |              |                 |          |
| Mean (SD)                              | 3.1 (1.3)       | 1.9 (1.3)    | 1.8 (1.1)       |          |
| 1                                      | 18 (12.6%)      | 76 (55.5%)   | 79 (56.4%)      |          |
| 2                                      | 33 (23.1%)      | 32 (23.4%)   | 29 (20.7%)      |          |
| 3                                      | 36 (25.2%)      | 12 (8.8%)    | 19 (13.6%)      |          |
| 4                                      | 26 (18.2%)      | 5 (3.6%)     | 9 (6.4%)        |          |
| 5                                      | 30 (21.0%)      | 12 (8.8%)    | 4 (2.9%)        |          |
| Treatment duration (days) <sup>b</sup> |                 |              |                 |          |
| Mean (SD)                              | 228.1 (129.0)   | 95.8 (129.2) | 84.2 (116.3)    |          |

<sup>a</sup> Of 5 possible treatments from Day 0 to Month 12 visits. The ranibizumab groups received sham PDT.

<sup>b</sup> The number of days between the first and the last treatment on or prior to Month 12 visit.

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**Table 7.2.1.3-3**  
**Number of Study Drug or Sham Injection Treatments Held**  
**Per Protocol-Specified Criteria During the First Treatment Year**  
**Safety Evaluable Subjects**

| Injection Held | Sham (N=140) | Lucentis (N=140) | Lucentis (N=140) | Lucentis (N=140) | Lucentis (N=140) | Lucentis (N=140) |
|----------------|--------------|------------------|------------------|------------------|------------------|------------------|
| Mean           | 0.1 (0.4)    | 0.1 (0.4)        | 0.1 (0.4)        | 0.0 (0.2)        | 0.0 (0.2)        | 0.2 (0.7)        |
| 0              | 224 (94.9%)  | 227 (95.4%)      | 229 (95.8%)      | 140 (97.9%)      | 131 (95.6%)      | 129 (92.1%)      |
| 1              | 7 (3.0%)     | 9 (3.8%)         | 7 (2.9%)         | 2 (1.4%)         | 6 (4.4%)         | 6 (4.3%)         |
| 2              | 3 (1.3%)     | 0                | 2 (0.8%)         | 1 (0.7%)         | 0                | 3 (2.1%)         |
| 3              | 1 (0.4%)     | 1 (0.4%)         | 0                | 0                | 0                | 0                |
| 4              | 1 (0.4%)     | 1 (0.4%)         | 1 (0.4%)         | 0                | 0                | 0                |
| 5              | 0            | 0                | 0                | 0                | 0                | 2 (1.4%)         |

**Reviewer's Comment:**

The vast majority, more than 92% of patients in each treatment group, did not require that treatments be held due to the protocol-specified dose-holding criteria.

**Table 7.2.1.3-4**  
**Study Drug or Sham Injection Held per Protocol-Specified Criteria by Criterion Met**  
**First Treatment Year: Safety Evaluable Subjects**

| Criterion                          | Sham (N=140) | Lucentis (N=140) | Lucentis (N=140) | Lucentis (N=140) | Lucentis (N=140) | Lucentis (N=140) |
|------------------------------------|--------------|------------------|------------------|------------------|------------------|------------------|
| Any Treatment Held                 | 12 (8.6%)    | 11 (7.9%)        | 10 (7.1%)        | 3 (2.1%)         | 6 (4.3%)         | 11 (7.9%)        |
| Intraocular inflammation           | 0            | 2 (1.4%)         | 4 (2.9%)         | 0                | 1 (0.7%)         | 3 (2.1%)         |
| Visual acuity loss                 | 6 (4.3%)     | 1 (0.7%)         | 1 (0.7%)         | 1 (0.7%)         | 0                | 0                |
| IOP elevation                      | 0            | 0                | 1 (0.7%)         | 0                | 1 (0.7%)         | 2 (1.4%)         |
| Vitreous hemorrhage                | 0            | 2 (1.4%)         | 0                | 0                | 0                | 0                |
| Sensory retinal detachment / break | 1 (0.7%)     | 1 (0.7%)         | 1 (0.7%)         | 0                | 1 (0.7%)         | 0                |
| Subfoveal hemorrhage               | 5 (3.6%)     | 1 (0.7%)         | 0                | 2 (1.4%)         | 0                | 2 (1.4%)         |
| Local or systemic infection        | 0            | 4 (2.9%)         | 2 (1.4%)         | 0                | 2 (1.4%)         | 4 (2.9%)         |
| Intraocular surgery                | 0            | 0                | 2 (1.4%)         | 0                | 1 (0.7%)         | 1 (0.7%)         |

Note: Tabulation was based on the 13 scheduled injections from Day 0 to Month 12. Multiple injections that were held because of the same criterion for a given subject were counted once in the overall incidence for the criterion. Multiple occurrences of injections held in a subject were counted once in the overall incidence.

**Reviewer's Comment:**

Approximately 3% of subjects in each treatment group in Study FV2598g required that at least one treatment be held due to the protocol-specified dose-holding criteria. In the sham treatment group, the reason for dose holding was most frequently visual acuity loss or subfoveal hemorrhage. In the ranibizumab treatment groups, no single criterion was met in the majority of cases.

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*In Study FVF2587g, treatments were held for protocol-specified holding criteria least often in the verteporfin PDT group and most frequently in the 0.5 mg ranibizumab group. Intraocular inflammation and local or systemic infection were the most frequent criteria met in the 0.5 mg ranibizumab group.*

#### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

##### 7.2.2.1 Other studies

No other studies were used to evaluate safety.

##### 7.2.2.2 Postmarketing experience

The product has not yet been marketed. No postmarketing data were used to evaluate safety.

##### 7.2.2.3 Literature

The applicant's literature search was complete, including important issues of safety and efficacy.

#### 7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience was adequate.

The pivotal studies, FVF2587g and FVF2598g, were adequate and well-controlled studies which demonstrated the efficacy of ranibizumab. An adequate number of subjects from relevant demographic groups were exposed to this formulation of ranibizumab to assess potential during the development program. The study designs were appropriate.

#### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Refer to the Pharmacology/Toxicology review for details.

#### 7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing and monitoring of study subject was adequate to elicit adverse events.

#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance and interaction were not performed due to the negligible systemic absorption of ranibizumab given by the intravitreal route of administration.

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#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant has made adequate efforts to detect specific adverse events for ranibizumab as a biologic and a VEGF inhibitor.

Serum samples for the evaluation of immunoreactivity to ranibizumab were obtained from subjects at screening and prior to study drug administration at Months 6 and 12. The assay demonstrated immunoreactivity in a small percentage of subjects in all three treatment groups prior to initial administration of study drug, possibly due to preexisting anti-Fab antibodies. There was no imbalance between ranibizumab-treated and sham-treated subjects regarding immunoreactivity to ranibizumab. Refer to Section 7.1.10 for details. Analyses of potential side effects related to systemic VEGF inhibition focused on the incidence of hypertension, arterial thromboembolic events and non-ocular hemorrhage.

**Table 7.2.7-1 Serious Adverse Events Potentially Related to Systemic VEGF Inhibition during the First Treatment Year:  
Studies FV2598g and FV2587g**

|                                     | 2 (0.8%) | 8 (3.4%) | 9 (3.8%) | 3 (1.1%) | 4 (1.5%) | 8 (5.1%) |
|-------------------------------------|----------|----------|----------|----------|----------|----------|
| Hypertension events                 | 0        | 1 (0.4%) | 0        | 0        | 0        | 0        |
| Arterial thromboembolic events      | 2 (0.8%) | 5 (2.1%) | 8 (3.3%) | 2 (1.4%) | 2 (1.4%) | 4 (2.9%) |
| Non-ocular hemorrhages              | 0        | 1 (0.4%) | 0        | 0        | 2 (1.5%) | 3 (2.1%) |
| Other potentially associated events | 0        | 1 (0.4%) | 1 (0.4%) | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |

Note: Multiple occurrences of the same type of event for a subject were counted once in the overall incidence.

#### Reviewer's Comment:

In the two phase 3 studies, a small trend in the occurrence of serious adverse events potentially related to systemic VEGF inhibition was noted, particularly in the ranibizumab 0.5-mg dose group. This reflects trends in serious arterial thromboembolic events and, to a lesser extent, in serious non-ocular hemorrhages (but not in serious hypertension or proteinuria). No imbalance in overall adverse events potentially related to systemic VEGF inhibition was observed among treatment groups.

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#### 7.2.8 Assessment of Quality and Completeness of Data

The data presented were complete and of good quality.

#### 7.2.9 Additional Submissions, Including Safety Update

The sponsor has submitted the following additional submissions of clinical safety and efficacy data during the review cycle. Amendments 003 and 006 were submitted in response to reviewer requests for additional analyses of the safety database. These amendments have been reviewed individually and the results incorporated into the rest of the review.

- Amendment 003 - Analysis of all of the thromboembolic adverse events in the ranibizumab trials including a comparison of risk factors and concomitant medications between patients who experienced thromboembolic events and all enrolled patients. (Submitted February 17, 2006)
- Amendment 006 - Request for information on all discontinued subjects regardless of attribution to study treatment, all serious adverse events and all adverse events occurring  $\geq 1\%$  of subjects in any treatment group for both Phase 3 studies. (Submitted March 17, 2006)
- Amendment 008 - Study FVF2598g Year 2 Data and Updated Draft Labeling (Submitted March 31 2006)

On April 28, 2006, the sponsor submitted the 120-Day Safety Update which is considered in this section. This update to the Summary of Clinical Safety includes additional safety information available from Study FVF2598g. Since the submission of the BLA, the collection and cleaning of second-treatment-year data from Study FVF2598g has been completed, and this update includes summaries based on final 2-year data from the study. No additional safety analyses are provided in the SCS update for Study FVF2587g because the trial is still ongoing, or for Study FVF2428g per prior agreement with the FDA. There are no updates to the safety analyses provided for Studies FVF2128g, FVF2425g, and FVF1770g because these trials were complete at the time of the original SCS.

All summaries presented within this report for Study FVF2598g are based on the safety-evaluable population (all subjects who received at least one ranibizumab or sham injection). In addition, subjects are grouped according to the actual treatment received, as defined from the safety analyses presented in the FVF2598g CSR Addendum. Subjects in the sham-injection group who crossed over to receive 0.5 mg ranibizumab per the sixth protocol amendment are included in the safety analyses. These subjects are included in the sham-injection group.

The original SCS included safety data from 1413 subjects, 976 of whom received treatment with ranibizumab. Of the six studies included in the SCS, Study FVF2598g was the largest with a total of 713 safety-evaluable subjects, 477 of whom received treatment with ranibizumab. As summarized in the original SCS, more than 5,800 ranibizumab injections and 2,700 sham injections were administered during the first treatment year of Study FVF2598g.

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Table 7.2.9-1 Extent of Study Drug Exposure: Study FVF2598g

| Original SCS                           |               |               |               |
|----------------------------------------|---------------|---------------|---------------|
| Number of injections <sup>a</sup>      |               |               |               |
| Total                                  | 2765          | 2952          | 2929          |
| Mean (SD) <sup>b</sup>                 | 11.7 (2.7)    | 12.4 (1.9)    | 12.3 (2.2)    |
| Treatment duration (days) <sup>c</sup> |               |               |               |
| Mean (SD)                              | 332.7 (80.0)  | 350.6 (54.7)  | 346.2 (61.5)  |
| Update to SCS                          |               |               |               |
| Number of injections <sup>a</sup>      |               |               |               |
| Total                                  | 4709          | 5248          | 5195          |
| Mean (SD) <sup>b</sup>                 | 20.0 (6.3)    | 22.1 (4.4)    | 21.7 (5.0)    |
| Treatment duration (days) <sup>c</sup> |               |               |               |
| Mean (SD)                              | 590.1 (191.2) | 651.4 (130.2) | 639.9 (148.2) |

<sup>a</sup> Intravitreal ranibizumab injection or sham injection <sup>b</sup> Number of injections per subject, or 24 scheduled injections during the 2-year treatment period. The summary includes ranibizumab injections received by subjects in the sham-injection group after crossover and a Month 24 injection received by Subject 144001 in the 0.5-mg group. <sup>c</sup> Number of days between the first and the last injection during the study period.

#### Reviewer's Comments:

The extent of study drug exposure was well balanced between the treatment groups in the first and second years of the study.

Table 7.2.9-3 Treatment and Study Discontinuations during the 2-Year Treatment Period: Safety Evaluable Subjects - Study FVF2598g

| Crossed over to receive 0.5 mg ranibizumab                  | 12 (5.1%)  | --                    | --                     |
|-------------------------------------------------------------|------------|-----------------------|------------------------|
| At Month 22                                                 | 5 (2.1%)   | --                    | --                     |
| At Month 23                                                 | 7 (3.0%)   | --                    | --                     |
| Discontinued treatment <sup>a</sup>                         | 66 (28.0%) | 30 (12.6%)            | 32 (13.4%)             |
| Death                                                       | 5 (2.1%)   | 5 (2.1%)              | 3 (1.3%) <sup>b</sup>  |
| Adverse event                                               | 13 (5.5%)  | 8 (3.4%)              | 14 (5.9%) <sup>b</sup> |
| Lost to follow-up                                           | 2 (0.8%)   | 2 (0.8%)              | 3 (1.3%)               |
| Subject's decision                                          | 24 (10.2%) | 17 (7.1%)             | 13 (5.4%)              |
| Physician's decision                                        | 1 (0.4%)   | 1 (0.4%) <sup>*</sup> | 2 (0.8%)               |
| Subject non-compliance                                      | 1 (0.4%)   | 0                     | 0                      |
| Subject's condition mandated other therapeutic intervention | 23 (9.7%)  | 1 (0.4%)              | 0                      |

<sup>a</sup> Some subjects remained in the study after treatment discontinuation.

<sup>b</sup> Three subjects discontinued from treatment because of an adverse event that resulted in death (the primary reason for study discontinuation).

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Table 7.2.9-4 Deaths during the 2-Year Treatment Period:  
Safety Evaluable Subjects - Study FVF2598g

|         | 0.3 mg<br>(N=239) | 0.5 mg<br>(N=239) |
|---------|-------------------|-------------------|
| Overall | 6 (2.5%)          | 5 (2.1%)          |
| Year 1  | 0                 | 1 (0.4%)          |
| Year 2  | 6 (2.5%)          | 4 (1.7%)          |

Table 7.2.9-5 Primary Cause of Deaths that Occurred during the 2-Year Treatment Period:  
Study FVF2598g

| Time Period | Treatment | Subject | Primary Cause of Death                                             | Number of Deaths | Number of Deaths in Study Population |
|-------------|-----------|---------|--------------------------------------------------------------------|------------------|--------------------------------------|
| Year 1      | 0.3 mg    | 78/F    | Heart attack                                                       | 12               | 11                                   |
|             |           | 78/F    | Small bowel infarct                                                | 178              | 24                                   |
|             | 0.5 mg    | 90/F    | Chronic asthma / COPD                                              | 155              | 2                                    |
| Year 2      | Sham      | 74/F    | Unknown cause                                                      | 481              | 3                                    |
|             |           | 88/M    | Congestive heart failure                                           | 724              | 91                                   |
|             |           | 76/F    | Cerebrovascular accident                                           | 673              | 35                                   |
|             |           | 77/M    | Acute or chronic renal failure                                     | 656              | 45                                   |
|             | 0.3 mg    | 80/M    | Cerebral vascular accident; bilateral parietal lobe and cerebellum | 576              | 31                                   |
|             |           | 71/M    | Acute respiratory failure                                          | 400              | 67                                   |
|             |           | 91/F    | Unknown                                                            | 669              | 99                                   |
|             |           | 77/F    | Complications of Non-Hodgkin's Lymphoma                            | 752              | 425                                  |
|             | 0.5 mg    | 91/F    | Myocardial infarction                                              | 570              | 23                                   |
|             |           | 81/M    | Pneumonia                                                          | 617              | 47                                   |
|             |           | 72/M    | Closed head injury resulting from automobile accident              | 627              | 57                                   |
|             |           | 87/F    | Stroke                                                             | 667              | 461                                  |
|             |           | 76/M    | Sepsis                                                             | 496              | 16                                   |
|             |           | 85/F    | Hemorrhagic cerebrovascular accident                               | 428              | 14                                   |

**Reviewer's Comment:**

An additional 14 deaths occurred in the second treatment year. Overall, no imbalance was noted between the treatment groups in the numbers or causes of death during the 2 year treatment period. The primary causes of death were common events in this elderly population of patients.

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Table 7.2.9-6 Ocular Serious Adverse Events in the Study Eye during the 2-Year Treatment Period (Occurring in > 1 Subject Overall): Study FVF2598g

| Adverse Event                                     | 0.5 mg                | 2.0 mg                | 4.0 mg    |
|---------------------------------------------------|-----------------------|-----------------------|-----------|
| Total Ocular Events in the Study Eye <sup>a</sup> | 17 (7.2%)             | 20 (8.4%)             | 21 (8.8%) |
| Choroidal neovascularization                      | 2 (0.8%)              | 0                     | 0         |
| Detachment of RPE                                 | 0                     | 1 (0.4%)              | 1 (0.4%)  |
| Endophthalmitis                                   | 0                     | 2 (0.8%)              | 2 (0.8%)  |
| IOP increased                                     | 0                     | 1 (0.4%)              | 2 (0.8%)  |
| Iridocyclitis                                     | 0                     | 1 (0.4%)              | 2 (0.8%)  |
| Macular degeneration                              | 6 (2.5%)              | 1 (0.4%)              | 2 (0.8%)  |
| Medication error                                  | 0                     | 1 (0.4%)              | 1 (0.4%)  |
| Retinal detachment                                | 1 (0.4%) <sup>b</sup> | 1 (0.4%) <sup>c</sup> | 0         |
| Retinal hemorrhage                                | 4 (1.7%)              | 2 (0.8%)              | 1 (0.4%)  |
| Retinal tear                                      | 0                     | 1 (0.4%)              | 1 (0.4%)  |
| Uveitis                                           | 0                     | 1 (0.4%)              | 1 (0.4%)  |
| Visual acuity reduced                             | 3 (1.3%)              | 3 (1.3%)              | 1 (0.4%)  |
| Vitreous hemorrhage                               | 2 (0.8%)              | 1 (0.4%)              | 1 (0.4%)  |

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.

a Represents the number of subjects with at least one ocular adverse event in the study eye.

b Rhegmatogenous retinal detachment

c Exudative retinal detachment

#### Reviewer's Comment:

Generally, serious ocular adverse events occurred in a very low percentage of subjects regardless of treatment group. The results are similar to those seen in the first treatment year.

Given the numbers of intravitreal injections in each treatment group (See Table 7.2.9-1), the per-injection rates of endophthalmitis, traumatic cataract, intraocular inflammation and retinal detachment were all very low approximately  $\leq 0.10\%$  per injection in each dose group.

Conjunctival hemorrhage, increased intraocular pressure, vitreous floaters, and vitritis occurred more frequently in the ranibizumab groups than in the sham injection group.

Choroidal neovascularization, macular degeneration, retinal hemorrhage, and subretinal fibrosis, manifestations of active neovascular AMD lesions were more common in the sham-injection group than in the ranibizumab groups.

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Table 7.2.9-7 Non-Ocular Serious Adverse Events during the 2-Year Treatment Period  
 (Occurring in > 1 Subject Overall) Study FVF2598g

|                                        | 73 (30.4%) | 82 (34.5%)            | 76 (31.8%) |
|----------------------------------------|------------|-----------------------|------------|
| Total Non-Ocular Events                | 73 (30.4%) | 82 (34.5%)            | 76 (31.8%) |
| Abdominal pain upper                   | 3 (1.3%)   | 0                     | 0          |
| Acute myocardial infarction            | 0          | 3 (1.3%) <sup>b</sup> | 0          |
| Angina unstable                        | 0          | 2 (0.8%)              | 0          |
| Arthritis                              | 0          | 2 (0.8%)              | 0          |
| Asthma                                 | 1 (0.4%)   | 1 (0.4%)              | 2 (0.8%)   |
| Atrial fibrillation                    | 4 (1.7%)   | 3 (1.3%)              | 5 (2.1%)   |
| B-cell lymphoma                        | 2 (0.8%)   | 0                     | 0          |
| Back pain                              | 0          | 2 (0.8%)              | 0          |
| Breast cancer                          | 2 (0.8%)   | 0                     | 0          |
| Cardiac failure congestive             | 6 (2.5%)   | 4 (1.7%)              | 1 (0.4%)   |
| Carotid artery stenosis                | 0          | 0                     | 2 (0.8%)   |
| Cellulitis                             | 5 (2.1%)   | 1 (0.4%)              | 0          |
| Cerebrovascular accident               | 3 (1.3%)   | 3 (1.3%)              | 6 (2.5%)   |
| Chest pain                             | 3 (1.3%)   | 4 (1.7%)              | 3 (1.3%)   |
| Chronic obstructive pulmonary disease  | 2 (0.8%)   | 4 (1.7%)              | 4 (1.7%)   |
| Coronary artery disease                | 5 (2.1%)   | 2 (0.8%)              | 4 (1.7%)   |
| Coronary artery occlusion              | 1 (0.4%)   | 0                     | 2 (0.8%)   |
| Deep vein thrombosis                   | 0          | 3 (1.3%)              | 0          |
| Dehydration                            | 0          | 1 (0.4%)              | 2 (0.8%)   |
| Diverticulitis                         | 1 (0.4%)   | 2 (0.8%)              | 4 (1.7%)   |
| Gout                                   | 2 (0.8%)   | 0                     | 0          |
| Hip fracture                           | 1 (0.4%)   | 5 (2.1%)              | 1 (0.4%)   |
| Lobar pneumonia                        | 1 (0.4%)   | 2 (0.8%)              | 0          |
| Lumbar spinal stenosis                 | 2 (0.8%)   | 0                     | 0          |
| Lung neoplasm malignant                | 3 (1.3%)   | 2 (0.8%)              | 2 (0.8%)   |
| Myocardial infarction                  | 4 (1.7%)   | 4 (1.7%)              | 2 (0.8%)   |
| Non-cardiac chest pain                 | 0          | 0                     | 2 (0.8%)   |
| Osteoarthritis                         | 3 (1.3%)   | 1 (0.4%)              | 0          |
| Pneumonia                              | 4 (1.7%)   | 9 (3.8%)              | 7 (2.9%)   |
| Renal cell carcinoma stage unspecified | 2 (0.8%)   | 0                     | 0          |
| Sepsis                                 | 0          | 0                     | 3 (1.3%)   |
| Syncope                                | 6 (2.5%)   | 3 (1.3%)              | 2 (0.8%)   |
| Transient ischemic attack              | 1 (0.4%)   | 2 (0.8%)              | 3 (1.3%)   |

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.

a Represents the number of subjects with at least one non-ocular serious adverse event.

b Includes Subject 101020 with a serious adverse event of acute myocardial infarction even though the event was removed from final study database based on an investigator correction form submitted after the completion of the FVF2598g CS.

c The sham-treated subject (118004) who experiences a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event. d Includes one case reported as a cerebral ischemia.

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**Reviewer's Comment:**

*The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. The percentages of subjects with non-ocular serious adverse events were well balanced among the treatment groups and similar to those seen in the first treatment year.*

**Table 7.2.9-8 Ocular Adverse Events in the Study Eye that Led to Discontinuation from Study or from Treatment during the 2-Year Treatment Period: Study FVF2598g**

| MedDRA                       | 15 (6.4%) | 6 (2.5%) | 7 (2.9%) |
|------------------------------|-----------|----------|----------|
| Total <sup>a</sup>           | 15 (6.4%) | 6 (2.5%) | 7 (2.9%) |
| Choroidal neovascularization | 7 (3.0%)  | 0        | 0        |
| Conjunctivitis allergic      | 0         | 0        | 1 (0.4%) |
| Eye pain                     | 0         | 0        | 2 (0.8%) |
| Glaucoma                     | 0         | 0        | 1 (0.4%) |
| Hypopyon                     | 0         | 0        | 1 (0.4%) |
| Indocyclitis                 | 0         | 0        | 2 (0.8%) |
| Iris adhesions               | 0         | 0        | 1 (0.4%) |
| Iritis                       | 0         | 3 (1.3%) | 0        |
| Macular degeneration         | 6 (2.5%)  | 0        | 0        |
| Macular hole                 | 0         | 1 (0.4%) | 0        |
| Maculopathy                  | 0         | 1 (0.4%) | 0        |
| Retinal detachment           | 1 (0.4%)  | 0        | 0        |
| Retinal hemorrhage           | 4 (1.7%)  | 1 (0.4%) | 0        |
| Retinal tear                 | 1 (0.4%)  | 0        | 0        |
| Uveitis                      | 0         | 0        | 2 (0.8%) |
| Visual acuity reduced        | 2 (0.8%)  | 0        | 0        |
| Vitreous detachment          | 1 (0.4%)  | 0        | 0        |
| Vitreous floaters            | 0         | 0        | 1 (0.4%) |
| Vitritis                     | 0         | 0        | 1 (0.4%) |

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.

<sup>a</sup> Represents the number of subjects with at least one ocular adverse event in the study eye that led to discontinuation of study or treatment.

**Reviewer's Comment:**

*There was a larger discontinuation rate in the sham-injection group than in either ranibizumab group usually due to signs and symptoms of worsening macular degeneration.*

*Ranibizumab group discontinuations were caused by signs and symptoms that may be associated with intraocular inflammation. These findings are similar to those in the first treatment year.*

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Table 7.2.9-9 Ocular Adverse Events in the Study Eye during the 2-Year Treatment Period  
 (Occurring in  $\geq 10\%$  of Subjects in Any Group): Study FVF2598g

|                                       | 234 (98.7%) | 236 (99.2%) <sup>a</sup> | 235 (98.3%) |
|---------------------------------------|-------------|--------------------------|-------------|
| Total <sup>a</sup>                    | 234 (98.7%) | 236 (99.2%) <sup>a</sup> | 235 (98.3%) |
| Blepharitis                           | 21 (8.9%)   | 26 (10.9%)               | 32 (13.4%)  |
| Cataract NOS <sup>b</sup>             | 37 (15.7%)  | 37 (15.5%)               | 37 (15.5%)  |
| Choroidal neovascularization          | 40 (16.9%)  | 1 (0.4%)                 | 4 (1.7%)    |
| Conjunctival hemorrhage               | 156 (66.1%) | 184 (77.3%)              | 181 (75.7%) |
| Detachment of RPE                     | 36 (15.3%)  | 27 (11.3%)               | 22 (9.2%)   |
| Dry eye                               | 15 (6.4%)   | 16 (6.7%)                | 24 (10.0%)  |
| Eye irritation                        | 47 (19.9%)  | 38 (16.0%)               | 46 (19.2%)  |
| Eye pain                              | 79 (33.5%)  | 86 (36.1%)               | 89 (37.2%)  |
| Eye pruritus                          | 29 (12.3%)  | 23 (9.7%)                | 32 (13.4%)  |
| Foreign body sensation in eyes        | 34 (14.4%)  | 43 (18.1%)               | 45 (18.8%)  |
| Intraocular inflammation <sup>c</sup> | 25 (10.6%)  | 33 (13.9%)               | 43 (18.0%)  |
| IOP increased                         | 14 (5.9%)   | 57 (23.9%)               | 57 (23.8%)  |
| Lacrimation increased                 | 38 (16.1%)  | 41 (17.2%)               | 39 (16.3%)  |
| Macular degeneration                  | 159 (67.4%) | 111 (46.6%)              | 109 (45.6%) |
| Macular edema                         | 27 (11.4%)  | 6 (2.5%)                 | 12 (5.0%)   |
| Maculopathy                           | 27 (11.4%)  | 20 (8.4%)                | 23 (9.6%)   |
| Ocular hyperemia                      | 24 (10.2%)  | 24 (10.1%)               | 24 (10.0%)  |
| Retinal degeneration                  | 16 (6.8%)   | 25 (10.5%)               | 24 (10.0%)  |
| Retinal disorder                      | 22 (9.3%)   | 27 (11.3%)               | 30 (12.6%)  |
| Retinal exudates                      | 25 (10.6%)  | 21 (8.8%)                | 16 (6.7%)   |
| Retinal hemorrhage                    | 132 (55.9%) | 61 (25.6%)               | 58 (24.3%)  |
| Subretinal fibrosis                   | 37 (15.7%)  | 22 (9.2%)                | 15 (6.3%)   |
| Vision blurred                        | 20 (8.5%)   | 34 (14.3%)               | 22 (9.2%)   |
| Visual acuity reduced                 | 39 (16.5%)  | 26 (10.9%)               | 24 (10.0%)  |
| Visual disturbance                    | 21 (8.9%)   | 27 (11.3%)               | 33 (13.8%)  |
| Vitreous detachment                   | 42 (17.8%)  | 52 (21.8%)               | 53 (22.2%)  |
| Vitreous floaters                     | 24 (10.2%)  | 76 (31.9%)               | 71 (29.7%)  |
| Vitritis                              | 8 (3.4%)    | 17 (7.1%)                | 30 (12.6%)  |

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.

<sup>a</sup> Represents the number of subjects with at least one ocular adverse event in the study eye. <sup>b</sup> Includes the preferred terms: cataract, cataract cortical, cataract nuclear, cataract subcapsular, cataract traumatic, and lenticular opacities.

<sup>c</sup> Includes the preferred terms anterior chamber inflammation, hypopyon, iridocyclitis, iritis, uveitis and vitritis.

**Reviewer's Comment:**

The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. Conjunctival hemorrhage, increased intraocular pressure, vitreous floaters, and vitritis occurred more frequently in the ranibizumab groups than in the sham injection group. These findings are similar to those in the first treatment year.

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*Choroidal neovascularization, macular degeneration, retinal hemorrhage, and subretinal fibrosis, manifestations of active neovascular AMD lesions were more common in the sham-injection group than in the ranibizumab groups*

*The apparent dose dependent trend in the incidence of intraocular inflammation adverse events in the study eye was slightly increased in the 2-year treatment period data. Seven of the ranibizumab-treated subjects (1.5%) experienced at least one serious intraocular inflammation adverse event in the study eye. All of the serious intraocular inflammation adverse events were considered by the investigator to be related to study drug. Six of the seven subjects had study treatment held or discontinued from study treatment because of serious intraocular inflammation. One subject in the ranibizumab 0.5-mg group was reported to have serious uveitis and was treated with intravitreal antibiotics. The sponsor considered this adverse event a presumed case of endophthalmitis.*

*Elevated intraocular pressure adverse events were noted more frequently in the ranibizumab treated groups. Most events were reported as mild or moderate in severity though three ranibizumab-treated subjects had severe events. For those events that required treatment, medication was used most frequently though paracenteses and anterior chamber taps were required in eight of the 305 reported events.*

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**Table 7.2.9-10 Non-Ocular Adverse Events in the Study Eye during the 2-Year Treatment Period (Occurring in  $\geq 5\%$  of Subjects in Any Group): Study FVF2598g**

|                                   | 214 (90.1%) | 228 (95.8%) <sup>a</sup> | 228 (95.8%) |
|-----------------------------------|-------------|--------------------------|-------------|
| Total *                           | 214 (90.1%) | 228 (95.8%) <sup>a</sup> | 228 (95.8%) |
| Anemia                            | 19 (8.1%)   | 17 (7.1%)                | 18 (7.5%)   |
| Anxiety                           | 7 (3.0%)    | 10 (4.2%)                | 12 (5.0%)   |
| Arthralgia                        | 21 (8.9%)   | 26 (10.9%)               | 27 (11.3%)  |
| Arthritis                         | 20 (8.5%)   | 17 (7.1%)                | 19 (7.9%)   |
| Back pain                         | 22 (9.3%)   | 24 (10.1%)               | 22 (9.2%)   |
| Blood pressure increased          | 18 (7.6%)   | 16 (6.7%)                | 20 (8.4%)   |
| Bronchitis                        | 20 (8.5%)   | 23 (9.7%)                | 25 (10.5%)  |
| Chest pain                        | 13 (5.5%)   | 10 (4.2%)                | 9 (3.8%)    |
| Constipation                      | 18 (7.6%)   | 15 (6.3%)                | 13 (5.4%)   |
| Contusion                         | 20 (8.5%)   | 10 (4.2%)                | 9 (3.8%)    |
| Cough                             | 17 (7.2%)   | 23 (9.7%)                | 25 (10.5%)  |
| Depression                        | 16 (6.8%)   | 12 (5.0%)                | 14 (5.9%)   |
| Diarrhea                          | 20 (8.5%)   | 18 (7.6%)                | 10 (4.2%)   |
| Dizziness                         | 23 (9.7%)   | 18 (7.6%)                | 11 (4.6%)   |
| Dyspnea                           | 6 (2.5%)    | 12 (5.0%)                | 8 (3.3%)    |
| Edema peripheral                  | 14 (5.9%)   | 17 (7.1%)                | 10 (4.2%)   |
| Gastroesophageal reflux disease   | 12 (5.1%)   | 15 (6.3%)                | 9 (3.8%)    |
| Headache                          | 24 (10.2%)  | 36 (15.1%)               | 24 (10.0%)  |
| Herpes zoster                     | 5 (2.1%)    | 13 (5.5%)                | 10 (4.2%)   |
| Hypercholesterolemia              | 11 (4.7%)   | 10 (4.2%)                | 13 (5.4%)   |
| Hypertension                      | 38 (16.1%)  | 41 (17.2%)               | 39 (16.3%)  |
| Influenza                         | 12 (5.1%)   | 23 (9.7%)                | 19 (7.9%)   |
| Insomnia                          | 13 (5.5%)   | 10 (4.2%)                | 14 (5.9%)   |
| Nasopharyngitis                   | 31 (13.1%)  | 32 (13.4%)               | 38 (15.9%)  |
| Nausea                            | 13 (5.5%)   | 21 (8.8%)                | 21 (8.8%)   |
| Pain in extremity                 | 14 (5.9%)   | 15 (6.3%)                | 13 (5.4%)   |
| Pneumonia                         | 13 (5.5%)   | 18 (7.6%)                | 11 (4.6%)   |
| Sinusitis                         | 13 (5.5%)   | 18 (7.6%)                | 20 (8.4%)   |
| Upper respiratory tract infection | 23 (9.7%)   | 36 (15.1%)               | 18 (7.5%)   |
| Urinary tract infection           | 18 (7.6%)   | 21 (8.8%)                | 17 (7.1%)   |

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.

\* Represents the number of subjects with at least one ocular adverse event in the study eye.

**Reviewer's Comment:**

*The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. The reported adverse events during the 2-year treatment period were consistent with those seen in an elderly population and the first treatment year results.*

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#### Reviewer's Comment:

The overall 2-year safety profile in Study FVF2598g was similar to that observed based on first-treatment-year data. The most common adverse events in the study eye observed more frequently in the ranibizumab groups than in the sham-injection group were conjunctival hemorrhage, increased intraocular pressure and vitreous floaters.

The dose dependent association of ranibizumab and intraocular inflammation noted during the first treatment year persisted in the second treatment year. Cumulative 2-year rates of reported intraocular inflammation adverse events in the study eye of 13.9% and 18.0% in the 0.3-mg and 0.5-mg ranibizumab groups compared with the sham-injection group, 10.6%. The observed intraocular inflammation adverse events were usually mild in severity and occurrence was well-balanced among the subgroups studied. Serious intraocular inflammation adverse events only occurred in the ranibizumab groups with a cumulative rate of  $\leq 1.7\%$  during the 2-year treatment period.

Table 7.2.9-11 APTC Arterial Thromboembolic Events during the 2-Year Treatment Period: Safety-Evaluable Subjects - Study FVF2598g

| Event                          | Sham (n=239)            | 0.3 mg (n=239)        | 0.5 mg (n=239)        |
|--------------------------------|-------------------------|-----------------------|-----------------------|
| Total                          | 9 (3.8%)                | 11 (4.6%)             | 11 (4.6%)             |
| Vascular deaths                | 4 (1.7%) <sup>a</sup>   | 3 (1.3%) <sup>b</sup> | 3 (1.3%)              |
| Nonfatal myocardial infarction | 4 (1.7%)                | 6 (2.5%) <sup>c</sup> | 3 (1.3%)              |
| Nonfatal ischemic stroke       | 2 (0.8%) <sup>d,e</sup> | 3 (1.3%) <sup>b</sup> | 5 (2.1%) <sup>f</sup> |
| Nonfatal hemorrhagic stroke    | 0                       | 0                     | 1 (0.4%) <sup>d</sup> |

Note: Antiplatelet-Trialists' Collaboration. BMJ. 1994 Jan 8; 308(6921):81-106.

a Subject 136007 had a prior non-fatal ischemic stroke.

b Subject 101019 had a non-fatal ischemic stroke and died of an unknown cause.

c Subject 109001 had two events of MI.

d Subject 158001 had an MI and a hemorrhagic stroke, both non-fatal.

e The sham-treated subject (118004) who suffered a subacute parietooccipital lobe CVA (reported as an ocular serious adverse event) had received a single injection of ranibizumab 0.5 mg in error approximately 8 months prior to the stroke.

f Include 1 subject (200001) with cerebral ischemia who had MRI evidence of infarction in the pons and thalamus.

#### Reviewer's Comment:

In the second treatment year, the trend toward higher rates of APTC arterial thromboembolic events was somewhat decreased because the number of subjects who experienced events in the second treatment year was similar among the treatment groups (1 subjects [3.2%] in the sham-injection group, 8 subjects [3.4%] in the 0.3 mg ranibizumab group, and 6 subjects [2.6%] in the 0.5 mg ranibizumab group).

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### 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The trend in intraocular inflammation adverse events observed during the first treatment year was also observed through the second treatment year of Study FVF2598g, with cumulative 2-year rates of reported intraocular inflammation adverse events in the study eye of 13.9% and 18.0% in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, compared with 10.6% in the sham-injection group. However, the reported intraocular inflammation adverse events were generally mild in severity. The incidence of intraocular inflammation adverse events did not differ substantially between the subgroups examined, and rates were lower in the second treatment year compared with the first treatment year. The incidence of intraocular inflammation adverse events was consistent with results based on slit lamp examination.

In Study FVF2598g, serious intraocular inflammation adverse events were observed only in the ranibizumab groups but were uncommon for both dose groups (< 1.7% cumulative rate over the 2-year treatment period).

The frequency of intraocular inflammation adverse events in the study eye was higher in the ranibizumab groups (10.2% in the 0.3-mg group and 15.0% in the 0.5-mg group) compared with the verteporfin PDT group (2.8%).

### 7.4 General Methodology

#### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

##### 7.4.1.1 Pooled data vs. individual study data

Table 7.4.1.1-1 Arterial Thromboembolic Events during the First Treatment Year:  
Studies FVF2598g and FVF2587g Pooled (Safety Evaluable Subjects)

| Total <sup>a</sup>          | 11 (2.9%)             | 11 (2.9%) | 15 (4.0%) |
|-----------------------------|-----------------------|-----------|-----------|
| Acute Coronary Syndrome     | 0                     | 1 (0.3%)  | 0         |
| Acute myocardial infarction | 0                     | 1 (0.3%)  | 0         |
| Angina pectoris             | 2 (0.5%)              | 3 (0.8%)  | 2 (0.5%)  |
| Angina unstable             | 0                     | 1 (0.3%)  | 0         |
| Cerebral infarction         | 0                     | 1 (0.3%)  | 0         |
| Cerebral ischemia           | 0                     | 0         | 1 (0.3%)  |
| Cerebrovascular accident    | 2 (0.5%) <sup>b</sup> | 1 (0.3%)  | 3 (0.8%)  |
| Embolism                    | 0                     | 0         | 1 (0.3%)  |
| Femoral artery occlusion    | 1 (0.3%)              | 0         | 0         |
| Intestinal infarction       | 0                     | 0         | 1 (0.3%)  |
| Myocardial infarction       | 2 (0.5%)              | 2 (0.5%)  | 4 (1.1%)  |
| Retinal artery occlusion    | 0                     | 1 (0.3%)  | 0         |

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| Arterial thromboembolic events |          |          |          |
|--------------------------------|----------|----------|----------|
| Transient ischemic attack      | 4 (1.1%) | 0        | 4 (1.1%) |
| Vascular graft occlusion       | 0        | 1 (0.3%) | 0        |
| Vascular occlusion             | 0        | 1 (0.3%) | 0        |

a Represents the number of subjects with at least one arterial thromboembolic event.

b A sham-treated subject in Study FVF2598g who experienced a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event.

**Reviewer's Comment:**

The adverse events which were seen more frequently in the ranibizumab 0.5 mg group versus control are highlighted. The number of subjects with an arterial thromboembolic event was small in the pooled analysis of studies FVF2598g and FVF2587g. A direct relationship between ranibizumab dose and arterial thromboembolic events can not be ruled out.

A sham-treated subject in Study FVF2598g who experienced a subacute parietooccipital CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event.

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Table 7.4.1.1-2 Potential Risk Factors and Baseline Concomitant Medication Use for Subjects with Arterial Thromboembolic Events versus All Subjects: Studies FV2598g and FV2587g Pooled (Safety-Evaluable Subjects)

| Potential Risk Factor                                            | Control                      |                         | Ranibizumab                  |                         |
|------------------------------------------------------------------|------------------------------|-------------------------|------------------------------|-------------------------|
|                                                                  | Subjects with ATE<br>n/N (%) | All Subjects<br>n/N (%) | Subjects with ATE<br>n/N (%) | All Subjects<br>n/N (%) |
| Age ≥ 75 years                                                   | 8 (72.7%)                    | 259 (68.3%)             | 8 (72.7%)                    | 262 (69.9%)             |
| Male                                                             | 7 (63.6%)                    | 143 (37.7%)             | 2 (18.2%)                    | 156 (41.0%)             |
| History of hypertension or hypertension at baseline <sup>a</sup> | 7 (63.6%)                    | 249 (65.7%)             | 9 (81.8%)                    | 263 (70.7%)             |
| History of ATE                                                   | 6 (54.5%)                    | 113 (29.8%)             | 8 (72.7%)                    | 117 (31.2%)             |
| History of atherosclerosis                                       | 7 (63.6%)                    | 123 (33.0%)             | 9 (81.8%)                    | 127 (33.9%)             |
| History of diabetes mellitus                                     | 3 (27.3%)                    | 46 (12.1%)              | 4 (36.4%)                    | 47 (12.5%)              |
| History of myocardial infarction                                 | 1 (9.1%)                     | 29 (7.7%)               | 2 (18.2%)                    | 22 (5.9%)               |
| History of stroke or TIA                                         | 2 (18.2%)                    | 31 (8.2%)               | 3 (27.3%)                    | 26 (6.9%)               |
| History of venous thrombosis                                     | 0                            | 9 (2.4%)                | 1 (9.1%)                     | 13 (3.5%)               |
| Baseline concomitant medication use                              |                              |                         |                              |                         |
| Aspirin                                                          | 6 (54.5%)                    | 161 (42.5%)             | 4 (36.4%)                    | 146 (38.9%)             |
| Pericarditis                                                     | 0                            | 0                       | 0                            | 0                       |
| Anti-platelet agents                                             | 4 (36.4%)                    | 167 (44.1%)             | 9 (81.8%)                    | 169 (44.8%)             |
| Anti-coagulant agents                                            | 2 (18.2%)                    | 27 (7.1%)               | 1 (9.1%)                     | 26 (6.9%)               |
| Lipid-lowering agents                                            | 4 (36.4%)                    | 153 (40.4%)             | 5 (45.5%)                    | 150 (40.0%)             |

a. A sham-treated subject in Study FV2598g who experienced a subacute pseudo-oculopathy CVA (reported as an ocular serious adverse event) had received a single injection of 0.5 mg ranibizumab in error approximately 8 months prior to the event. b. Hypertension at baseline was defined as systolic blood pressure >150 mmHg, diastolic blood pressure >100 mmHg, or a use of a concomitant medication indicated for hypertension.

#### Reviewer's Comment:

For all subjects, potential risk factors for ATEs and baseline concomitant medication use were well balanced across the treatment groups in terms of percentages.

The number of subjects with ATE was small making comparisons somewhat difficult. Though subjects in the ranibizumab 0.5 mg group with an ATE did not have the highest aspirin use, their aspirin use was higher than all subjects in the ranibizumab 0.3 mg group.

Subjects with an ATE in the ranibizumab 0.5 mg group generally had potential risk factors at a higher percentage than the group as a whole.

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#### 7.4.1.2 Combining data

Studies FVF2598g and FVF2587g were sufficiently similar to allow data to be combined by adding the numerator events and denominators of the treatment groups across the studies.

#### 7.4.2 Explorations for Predictive Factors

A detailed discussion of the adverse events is presented in Sections 7.1.1 through 7.1.6. No clear predictive factors for a drug-related adverse event were identified.

#### 7.4.3 Causality Determination

Due to the small number of patients, no determination of causality could be made regarding the adverse events in the Phase 3 studies.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The sponsor has performed adequate dose ranging studies during the drug development program. Lucentis (ranibizumab) 0.5 mg dose has been demonstrated to be safe and effective in two Phase 3 clinical trials. The dosing interval in the two pivotal Phase 3 trials was once monthly resulting in the improvement and maintenance of visual acuity and function, and for the reduction of vascular leakage and retinal edema, in patients with neovascular (wet) age-related macular degeneration.

### 8.2 Drug-Drug Interactions

No important drug-drug interactions have been identified.

### 8.3 Special Populations

The sponsor has adequately evaluated gender effects on both the safety and efficacy outcomes. Subgroup analyses did not reveal any differences in the primary efficacy endpoint between males and females. The safety profiles seen in males and females, including the types and rates of adverse events, are similar.

Trials for this indication were conducted in a population that was overwhelmingly elderly and Caucasian. This is reflective of the population in which age-related macular degeneration occurs and does not reflect a problem with study enrollment.

### 8.4 Pediatrics

The applicant requested a waiver of the pediatric study requirements for the original Biologics License Application. The waiver was requested because the disease under study age-related macular degeneration does not occur in the pediatric age group.

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#### 8.5 Advisory Committee Meeting

Not applicable. No Advisory Committee Meeting will be held regarding this application.

#### 8.6 Literature Review

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

#### 8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan has been submitted.

#### 8.8 Other Relevant Materials

Comments received from DDMAC and the Office of Drug Safety have been incorporated in the labeling review as appropriate.

### 9 OVERALL ASSESSMENT

#### 9.1 Conclusions

The submitted studies in BLA 125156 are sufficient to establish efficacy for the use of ranibizumab 0.5 mg injection in the treatment of the neovascular age-related macular degeneration. The two Phase 3 studies provide replicative demonstration that monthly ranibizumab injections are able to stabilize and prevent vision loss in patients with neovascular macular degeneration compared to monthly sham and verteporfin PDT treatment.

#### 9.2 Recommendation on Regulatory Action

BLA 125156 is recommended for approval from a clinical perspective for the treatment of patients with neovascular (wet) age-related macular degeneration with the labeling revisions within this review.

#### 9.3 Recommendation on Postmarketing Actions

##### 9.3.1 Risk Management Activity

Not applicable. No postmarketing risk management activity is recommended at this time.

##### 9.3.2 Required Phase 4 Commitments

1. Develop and validate assays to detect and characterize immune responses to ranibizumab:

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A. Develop and validate a confirmatory assay capable of detecting both IgG and IgM isotype responses.

B. Develop and validate an assay to detect neutralizing anti-ranibizumab antibodies.

The assay methodology and validation reports will be provided by September 28, 2007.

2. To characterize further the immune response to ranibizumab, serum samples collected in studies FVF2587g, FVF2598g, FVF3192g will be assayed using the validated methods described above in Postmarketing Commitment. The data obtained will be analyzed to discover and evaluate any association between immunoreactivity and dosing frequency as well as any potential impact of immunoreactivity on efficacy or safety outcomes.

Date of submission of protocol and statistical analysis plan: February 28, 2007

Date of submission of final study report: September 2008.

3. The need for an additional clinical study will be determined based on the results from the analysis described above.

9.3.3 Other Phase 4 Requests

Not applicable. There are no additional Phase 4 requests.

9.4 Labeling Review

Refer to the Appendix, Section 10.2 for the medical officer's labeling review.

9.5 Comments to Applicant

There are no comments pertaining to specific deficiencies.

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14 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

✓ \_\_\_\_\_ § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 644

| Electronic Acknowledgement Receipt          |                                                            |
|---------------------------------------------|------------------------------------------------------------|
| <b>EFS ID:</b>                              | 32152813                                                   |
| <b>Application Number:</b>                  | 15471506                                                   |
| <b>International Application Number:</b>    |                                                            |
| <b>Confirmation Number:</b>                 | 8014                                                       |
| <b>Title of Invention:</b>                  | USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS |
| <b>First Named Inventor/Applicant Name:</b> | George D. YANCOPOULOS                                      |
| <b>Customer Number:</b>                     | 96387                                                      |
| <b>Filer:</b>                               | Karl Bozicevic/Kimberly Zuehlke                            |
| <b>Filer Authorized By:</b>                 | Karl Bozicevic                                             |
| <b>Attorney Docket Number:</b>              | REGN-008CIPCON2                                            |
| <b>Receipt Date:</b>                        | 26-MAR-2018                                                |
| <b>Filing Date:</b>                         | 28-MAR-2017                                                |
| <b>Time Stamp:</b>                          | 12:17:48                                                   |
| <b>Application Type:</b>                    | Utility under 35 USC 111(a)                                |

### Payment information:

| Submitted with Payment |                      | no                                                |                                                          |                  |                  |
|------------------------|----------------------|---------------------------------------------------|----------------------------------------------------------|------------------|------------------|
| <b>File Listing:</b>   |                      |                                                   |                                                          |                  |                  |
| Document Number        | Document Description | File Name                                         | File Size(Bytes)/<br>Message Digest                      | Multi Part /.zip | Pages (if appl.) |
| 1                      | Transmittal Letter   | REGN-008CIPCON2_2018-03-26<br>_Supp_IDS_trans.pdf | 53230<br><br>9e2d9110a4c350f3e2cfa6b0c6d932d3fcd<br>1964 | no               | 2                |
| <b>Warnings:</b>       |                      |                                                   |                                                          |                  |                  |

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| <b>Information:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                    |                                               |                                          |    |     |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                    |                                               | 34a1e53105969b09202066ec75cb96568f5b46c8 |    |     |
| <b>Warnings:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                    |                                               |                                          |    |     |
| <b>Information:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                    |                                               |                                          |    |     |
| This is not an USPTO supplied IDS fillable form                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                    |                                               |                                          |    |     |
| 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Non Patent Literature                              | D9.pdf                                        | 2160139                                  | no | 99  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                    |                                               | e9e4195c672ae9ed0a526a351d6104038e2b804e |    |     |
| <b>Warnings:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                    |                                               |                                          |    |     |
| <b>Information:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                    |                                               |                                          |    |     |
| 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Non Patent Literature                              | D10.pdf                                       | 4911467                                  | no | 172 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                    |                                               | ef199fb6643a6e6f4a6347172a17a30b9f2d6580 |    |     |
| <b>Warnings:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                    |                                               |                                          |    |     |
| <b>Information:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                    |                                               |                                          |    |     |
| <b>Total Files Size (in bytes):</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                    |                                               | 7147798                                  |    |     |
| <p><b>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</b></p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b><br/> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b><br/> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b><br/> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p> |                                                    |                                               |                                          |    |     |

**Electronically Filed**

|                                                                                                                           |                      |                                                                     |
|---------------------------------------------------------------------------------------------------------------------------|----------------------|---------------------------------------------------------------------|
| <b>INFORMATION<br/>DISCLOSURE STATEMENT</b><br><br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, VA 22313-1450 | Attorney Docket      | REGN-008CIPCON2                                                     |
|                                                                                                                           | First Named Inventor | YANCOPOULOS, GEORGE D.                                              |
|                                                                                                                           | Application Number   | 15/471,506                                                          |
|                                                                                                                           | Confirmation No.     | 8014                                                                |
|                                                                                                                           | Filing Date          | March 28, 2017                                                      |
|                                                                                                                           | Group Art Unit       | 1647                                                                |
|                                                                                                                           | Examiner Name        | LOCKARD, JON MCCLELLAND                                             |
|                                                                                                                           | Title:               | <i>“Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders”</i> |

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. §1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and a copy of the cited documents are attached.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

**Statements**

☐ **No statement**

.....

☒ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

- ☒ **IDS Statement under 37 CFR § 1.97(e)(1):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or
- ☐ **IDS Statement under 37 CFR § 1.97(e)(2):** No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

**Fees**

- ☒ No fee is believed to be due.
- ☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of \$3,000.00 beyond that authorized on the credit card, but not more than \$3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON2.

Respectfully submitted,  
BOZICEVIC, FIELD & FRANCIS LLP

Date: 26 March 2018

By: /Karl Bozicevic, Reg. No. 28,807/  
Karl Bozicevic, Reg. No. 28,807

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|                                                                                                                                      |             |                       |                                     |                             |
|--------------------------------------------------------------------------------------------------------------------------------------|-------------|-----------------------|-------------------------------------|-----------------------------|
| APPLICATION NO.                                                                                                                      | FILING DATE | FIRST NAMED INVENTOR  | ATTORNEY DOCKET NO.                 | CONFIRMATION NO.            |
| 15/471,506                                                                                                                           | 03/28/2017  | George D. YANCOPOULOS | REGN-008CIPCON2                     | 8014                        |
| 96387 7590 04/03/2018<br>Regeneron - Bozicevic, Field & Francis<br>201 REDWOOD SHORES PARKWAY<br>SUITE 200<br>REDWOOD CITY, CA 94065 |             |                       | EXAMINER<br>LOCKARD, JON MCCLELLAND |                             |
|                                                                                                                                      |             |                       | ART UNIT<br>1647                    | PAPER NUMBER                |
|                                                                                                                                      |             |                       | NOTIFICATION DATE<br>04/03/2018     | DELIVERY MODE<br>ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

|                              |                                      |                                               |                                                  |
|------------------------------|--------------------------------------|-----------------------------------------------|--------------------------------------------------|
| <b>Office Action Summary</b> | <b>Application No.</b><br>15/471,506 | <b>Applicant(s)</b><br>YANCOPOULOS, GEORGE D. |                                                  |
|                              | <b>Examiner</b><br>JON M. LOCKARD    | <b>Art Unit</b><br>1647                       | <b>AIA (First Inventor to File) Status</b><br>No |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 19 May 2017.  
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims\***

- 5) ☒ Claim(s) 21-46 is/are pending in the application.  
5a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 6) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 7) ☒ Claim(s) 21-46 is/are rejected.
- 8) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 9) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

\* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see [http://www.uspto.gov/patents/init\\_events/pph/index.jsp](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

**Application Papers**

- 10) ☒ The specification is objected to by the Examiner.
- 11) ☒ The drawing(s) filed on 28 March 2017 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

- a) ☐ All    b) ☐ Some\*\*    c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)  
Paper No(s)/Mail Date attached.
- 3) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_.
- 4) ☐ Other: \_\_\_\_.

## **DETAILED ACTION**

### ***Status of Application, Amendments, and/or Claims***

1. The present application is being examined under the pre-AIA first to invent provisions.
2. The Preliminary Amendment filed on 19 May 2017 has been entered in full. Claims 1-20 have been cancelled, and claims 21-46 have been added. Therefore, claims 21-46 are pending and the subject of this Office Action.

### ***Information Disclosure Statement***

3. The information disclosure statements (IDS) filed 26 May 2017, 18 July 2017, 02 August 2017 and 26 March 2018 have been considered by the examiner.

### ***Specification***

4. The disclosure is objected to because of the following informalities: An updated status of the parent nonprovisional application should be included in the first sentence of the specification. Appropriate correction is suggested.

### ***Double Patenting***

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not

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patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

6. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

7. The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit <http://www.uspto.gov/forms/>. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to <http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

8. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 7,303,746. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '746 patent are drawn to methods for treating retinal neovascularization (an

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angiogenic eye disorder), comprising administering a fusion polypeptide which comprises the amino acid sequence of SEQ ID NO:16, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the '746 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

9. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 7,303,747. Although the conflicting claims are not identical as they differ in scope, they are not patentably distinct from each other because claims 1-6 of the '747 patent are drawn to methods for treating or ameliorating an angiogenic eye disorder, including choroidal neovascularization, vascular leak, or retinal edema, comprising administering a fusion polypeptide capable of binding endothelial growth factor (VEGF) to a patient in need thereof, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO:6, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the '747 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

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“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

10. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 7,306,799. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-6 of the ‘799 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration and diabetic retinopathy, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:6, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the ‘799 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

11. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 7,521,049. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-15 of the ‘049 patent are drawn to a method for treating an angiogenic eye disorder,

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including age-related macular degeneration, diabetic retinopathy, choroidal neovascularization, vascular leak, and/or retinal edema, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:23, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the '049 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

12. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 9,254,338. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-26 of the '338 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, choroidal neovascularization, vascular leak, and/or retinal edema, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the '338 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

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“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

13. Claims 21-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,669,069. Although the conflicting claims are not identical, as they recite different dosing schedules, they are not patentably distinct from each other because claims 1-12 of the ‘069 patent are drawn to a method for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization, comprising administering a fusion polypeptide having the amino acid sequence set forth in SEQ ID NO:2, which shares 100% sequence identity to the fusion protein of SEQ ID NO:2 (encoded by SEQ ID NO:1) of the instant application. While the ‘069 patent does not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules. The courts have determined that:

“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223,235, (CCPA 1955).

Therefore, the claims are overlapping in scope.

#### Summary

14. No claim is allowed.

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***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon M. Lockard whose telephone number is (571) 272-2717. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama, can be reached on (571) 272-2911. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JON M LOCKARD/  
Examiner, Art Unit 1647  
March 29, 2018

|                                                          |   |    |   |                        |                         |
|----------------------------------------------------------|---|----|---|------------------------|-------------------------|
| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b> |   |    |   | Application Number     | 15/471,506              |
|                                                          |   |    |   | Filing Date            | March 28, 2017          |
|                                                          |   |    |   | First Named Inventor   | YANCOPOULOS, GEORGE D.  |
|                                                          |   |    |   | Art Unit               | 1647                    |
|                                                          |   |    |   | Examiner Name          | LOCKARD, JON MCCLELLAND |
| Sheet                                                    | 1 | of | 1 | Attorney Docket Number | REGN-008CIPCON2         |

| U.S. PATENT DOCUMENTS |          |                                              |                          |                                                    |                                                                                 |
|-----------------------|----------|----------------------------------------------|--------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|
| Examiner Initial*     | Cite No. | Patent Number<br>Number-Kind Code (if known) | Issue Date<br>YYYY-MM-DD | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines, Where<br>Relevant Passages or Relevant<br>Figures Appear |
|                       | 1        |                                              |                          |                                                    |                                                                                 |

| U.S. PATENT APPLICATION PUBLICATIONS |          |                                                   |                                |                                                    |                                                                                 |
|--------------------------------------|----------|---------------------------------------------------|--------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|
| Examiner Initial*                    | Cite No. | Publication Number<br>Number-Kind Code (if known) | Publication Date<br>YYYY-MM-DD | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines, Where<br>Relevant Passages or Relevant<br>Figures Appear |
|                                      | 1        |                                                   |                                |                                                    |                                                                                 |

| FOREIGN PATENT DOCUMENTS |          |                                                                     |                                |                                                    |                                                                                 |   |
|--------------------------|----------|---------------------------------------------------------------------|--------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|---|
| Examiner Initial*        | Cite No. | Foreign Document Number<br>Country Code-Number-Kind Code (if known) | Publication Date<br>YYYY-MM-DD | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines, Where<br>Relevant Passages or Relevant<br>Figures Appear | T |
|                          | 1        |                                                                     |                                |                                                    |                                                                                 |   |

| NON PATENT LITERATURE DOCUMENTS |          |                                                                                                                                                                                                                                                                 |   |
|---------------------------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|
| Examiner Initials*              | Cite No. | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T |
| /J. L./                         | 1        | HEIER et al., "Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related macular Degeneration," Ophthalmology, 119:2537-2548 (2012)                                                                                                                           |   |

|                    |                 |                 |            |
|--------------------|-----------------|-----------------|------------|
| Examiner Signature | /JON M LOCKARD/ | Date Considered | 03/29/2018 |
|--------------------|-----------------|-----------------|------------|

EXAMINER: Initial if reference considered; whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.



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CONFIRMATION NO. 8014

| SERIAL NUMBER                                                                                                                                                                                                                                                                                                                                             | FILING or 371(c)<br>DATE                                                                                          | CLASS                             | GROUP ART UNIT                                                                                                                                                                                                                                                            | ATTORNEY DOCKET<br>NO.        |                                    |
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| 15/471,506                                                                                                                                                                                                                                                                                                                                                | 03/28/2017                                                                                                        | 424                               | 1647                                                                                                                                                                                                                                                                      | REGN-008CIPCON2               |                                    |
| <b>APPLICANTS</b><br>REGENERON PHARMACEUTICALS, INC., Tarrytown, NY<br><b>INVENTORS</b><br>George D. YANCOPOULOS, Yorktown Heights, NY;                                                                                                                                                                                                                   |                                                                                                                   |                                   |                                                                                                                                                                                                                                                                           |                               |                                    |
| <b>** CONTINUING DATA *****</b><br>This application is a CON of 14/972,560 12/17/2015 PAT 9669069<br>which is a CON of 13/940,370 07/12/2013 PAT 9254338<br>which is a CIP of PCT/US2012/020855 01/11/2012<br>which claims benefit of 61/432,245 01/13/2011<br>and claims benefit of 61/434,836 01/21/2011<br>and claims benefit of 61/561,957 11/21/2011 |                                                                                                                   |                                   |                                                                                                                                                                                                                                                                           |                               |                                    |
| <b>** FOREIGN APPLICATIONS *****</b><br><b>** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **</b><br>09/05/2017                                                                                                                                                                                                                                            |                                                                                                                   |                                   |                                                                                                                                                                                                                                                                           |                               |                                    |
| Foreign Priority claimed <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No<br>35 USC 119(a-d) conditions met <input type="checkbox"/> Yes <input type="checkbox"/> No<br>Verified and /JON MCCLELLAND<br>Acknowledged LOCKARD/<br>Examiner's Signature                                                                                  | <input type="checkbox"/> Met after Allowance<br>Initials                                                          | <b>STATE OR<br/>COUNTRY</b><br>NY | <b>SHEETS<br/>DRAWINGS</b><br>1                                                                                                                                                                                                                                           | <b>TOTAL<br/>CLAIMS</b><br>26 | <b>INDEPENDENT<br/>CLAIMS</b><br>2 |
| <b>ADDRESS</b><br>Regeneron - Bozicevic, Field & Francis<br>201 REDWOOD SHORES PARKWAY<br>SUITE 200<br>REDWOOD CITY, CA 94065<br>UNITED STATES                                                                                                                                                                                                            |                                                                                                                   |                                   |                                                                                                                                                                                                                                                                           |                               |                                    |
| <b>TITLE</b><br>USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS                                                                                                                                                                                                                                                                                |                                                                                                                   |                                   |                                                                                                                                                                                                                                                                           |                               |                                    |
| <b>FILING FEE<br/>RECEIVED</b><br>2220                                                                                                                                                                                                                                                                                                                    | FEES: Authority has been given in Paper<br>No. _____ to charge/credit DEPOSIT ACCOUNT<br>No. _____ for following: |                                   | <input type="checkbox"/> All Fees<br><input type="checkbox"/> 1.16 Fees (Filing)<br><input type="checkbox"/> 1.17 Fees (Processing Ext. of time)<br><input type="checkbox"/> 1.18 Fees (Issue)<br><input type="checkbox"/> Other _____<br><input type="checkbox"/> Credit |                               |                                    |

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|----------------------------------------------------------|---|----|---|------------------------|-------------------------|
| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b> |   |    |   | Application Number     | 15/471,506              |
|                                                          |   |    |   | Filing Date            | March 28, 2017          |
|                                                          |   |    |   | First Named Inventor   | YANCOPOULOS, GEORGE D.  |
|                                                          |   |    |   | Art Unit               | 1647                    |
|                                                          |   |    |   | Examiner Name          | LOCKARD, JON MCCLELLAND |
| Sheet                                                    | 1 | of | 1 | Attorney Docket Number | REGN-008CIPCON2         |

| U.S. PATENT DOCUMENTS |          |                                              |                          |                                                    |                                                                                 |
|-----------------------|----------|----------------------------------------------|--------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|
| Examiner Initial*     | Cite No. | Patent Number<br>Number-Kind Code (if known) | Issue Date<br>YYYY-MM-DD | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines, Where<br>Relevant Passages or Relevant<br>Figures Appear |
|                       | 1        |                                              |                          |                                                    |                                                                                 |

| U.S. PATENT APPLICATION PUBLICATIONS |          |                                                   |                                |                                                    |                                                                                 |
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| /J.L./                          | 1        | CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 21-756<br>MEDICAL REVIEW(S) (December 17, 2004)<br><URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen_medr.pdf>                                                            |   |
| /J.L./                          | 2        | CENTER FOR DRUG EVALUATION AND RESEARCH BLA APPLICATION NUMBER:<br>125156 MEDICAL REVIEW, (June 2006)<br><URL:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s000_Lucentis_MedR.pdf>                                                             |   |

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| Examiner Signature | /JON M LOCKARD/ | Date Considered | 03/29/2018 |
|--------------------|-----------------|-----------------|------------|

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**Inventor Information for 15/471506**

/J.L./

|                        |                  |                      |
|------------------------|------------------|----------------------|
| <b>Inventor Name</b>   | <b>City</b>      | <b>State/Country</b> |
| YANCOPOULOS, GEORGE D. | YORKTOWN HEIGHTS | NEW YORK             |

|                            |                          |                               |                                 |                                 |                              |                  |                            |                         |                      |                           |                           |
|----------------------------|--------------------------|-------------------------------|---------------------------------|---------------------------------|------------------------------|------------------|----------------------------|-------------------------|----------------------|---------------------------|---------------------------|
| <a href="#">Appln Info</a> | <a href="#">Contents</a> | <a href="#">Petition Info</a> | <a href="#">Atty/Agent Info</a> | <a href="#">Continuity Data</a> | <a href="#">Foreign Data</a> | <b>Inventors</b> | <a href="#">Applicants</a> | <a href="#">Address</a> | <a href="#">Fees</a> | <a href="#">Post Info</a> | <a href="#">Pre Grant</a> |
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15/471,506

/J.L./

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(FILE 'HOME' ENTERED AT 18:49:12 ON 29 MAR 2018)

FILE 'MEDLINE, SCISEARCH, EMBASE, BIOSIS' ENTERED AT 18:49:22 ON 29 MAR 2018

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L1      4773 S (FLT1 OR VEGFR1 OR (VEGF (W) R1)) (P) (FLK1 OR KDR OR VEGFR2
L2      43 S L1 AND ((CHIMER? OR FUSION) (S) VEGF)
L3      0 S L2 AND ((EYE OR OCULAR OR RETINA? OR MACULAR) (S) DOSORDER)
L4      0 S L2 AND ((EYE OR OCULAR OR RETINA? OR MACULAR) (S) DISORDER)
L5      102 S L1 (P) (CHIMER? OR FUSION)
L6      2 S L5 AND ((EYE OR OCULAR OR RETINA? OR MACULAR) (S) DISORDER)
L7      700 S (VEGF (W) TRAP) AND (EYE OR OCULAR OR RETINA? OR MACULAR)
L8      572 S (VEGF (W) TRAP) (P) (EYE OR OCULAR OR RETINA? OR MACULAR)
L9      353 S (VEGF (W) TRAP) (S) (EYE OR OCULAR OR RETINA? OR MACULAR)
L10     92 S L9 AND PD<=2011
L11     47 DUP REM L10 (45 DUPLICATES REMOVED)
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|----------------------------------------------------------|---|----|---|------------------------|------------------------|
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|                                                          |   |    |   | First Named Inventor   | YANCOPOULOS, GEORGE D. |
|                                                          |   |    |   | Art Unit               | N/A                    |
|                                                          |   |    |   | Examiner Name          | N/A                    |
| Sheet                                                    | 1 | of | 3 | Attorney Docket Number | REGN-008CIPCON2        |

| U.S. PATENT DOCUMENTS |          |                                              |                          |                                                    |                                                                                 |
|-----------------------|----------|----------------------------------------------|--------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|
| Examiner Initial*     | Cite No. | Patent Number<br>Number-Kind Code (if known) | Issue Date<br>YYYY-MM-DD | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines, Where<br>Relevant Passages or Relevant<br>Figures Appear |
|                       | 1        | 7396664                                      | 2008-07-08               | Daly et al.                                        |                                                                                 |

| U.S. PATENT APPLICATION PUBLICATIONS |          |                                                   |                                |                                                    |                                                                                 |
|--------------------------------------|----------|---------------------------------------------------|--------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|
| Examiner Initial*                    | Cite No. | Publication Number<br>Number-Kind Code (if known) | Publication Date<br>YYYY-MM-DD | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines, Where<br>Relevant Passages or Relevant<br>Figures Appear |
|                                      | 1        | 20050163798                                       | 2005-07-28                     | Papadopoulos et al.                                |                                                                                 |
|                                      | 2        | 20050260203                                       | 2005-11-24                     | Wiegand et al.                                     |                                                                                 |
|                                      | 3        | 20060058234                                       | 2006-03-16                     | Daly et al.                                        |                                                                                 |
|                                      | 4        | 20060172944                                       | 2006-08-03                     | Wiegand et al.                                     |                                                                                 |
|                                      | 5        | 20070190058                                       | 2007-08-16                     | Shams                                              |                                                                                 |
|                                      | 6        | 20030171320                                       | 2003-09-11                     | Guyer                                              |                                                                                 |

| FOREIGN PATENT DOCUMENTS |          |                                                                     |                                |                                                    |                                                                                 |   |
|--------------------------|----------|---------------------------------------------------------------------|--------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|---|
| Examiner Initial*        | Cite No. | Foreign Document Number<br>Country Code-Number-Kind Code (if known) | Publication Date<br>YYYY-MM-DD | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines, Where<br>Relevant Passages or Relevant<br>Figures Appear | T |
|                          | 1        | WO 2000/75319                                                       | 2000-12-14                     | Regeneron Pharmaceuticals, Inc.                    |                                                                                 |   |
|                          | 2        | WO 2007/022101 A2                                                   | 2007-02-22                     | Regeneron Pharmaceuticals, Inc.                    |                                                                                 |   |
|                          | 3        | WO 2008/063932                                                      | 2008-05-29                     | Genentech, Inc.                                    |                                                                                 |   |
|                          | 4        | JP 2010-509369                                                      | 2010-03-25                     | Genentech, Inc.                                    | See WO 2008/063932 for English Equivalent                                       |   |

| NON PATENT LITERATURE DOCUMENTS |          |                                                                                                                                                                                                                                                                  |   |
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| Examiner Initials*              | Cite No. | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.  | T |
|                                 | 1        | ANONYMOUS "Lucentis (ranibizumab injection) Intravitreal Injection" pp. 103 (June 2006)                                                                                                                                                                          |   |
|                                 | 2        | Information from ClinicalTrials.gov archive View of NCT00637377 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2)" <i>ClinicalTrials.gov</i> . Web. 2010-11-30.   |   |
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|                                 | 6        | DO et al., "The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema" Ophthalmology 118(9):1819-1826 (September 2011)                                                                                                      |   |  |
|                                 | 7        | THE EYETECH STUDY GROUP, "Anti-Vascular Endothelial Growth Factor Therapy for Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration" American Academy of Ophthalmology, 110(5):979-986 (May 2003)                                       |   |  |
|                                 | 8        | HEIER et al., " rhuFab V2 (anti-VEGF Antibody) for Treatment of Exudative AMD" Symposium 8:Experimental and Emerging Treatments for Choroidal Neovascularization, 10 pp (2002)                                                                                         |   |  |
|                                 | 9        | HEIER et al., "RhuFab V2 in Wet AMD - 6 Month Continued Improvement Following Multiple Intravitreal Injections" Invest Ophthalmol Vis Sci, 44:E-Abstract 972 (2003)                                                                                                    |   |  |
|                                 | 10       | Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)" version available and updated on 17 March 2008.                                                                |   |  |
|                                 | 11       | Information from ClinicalTrials.gov archive on the view of NCT00509795 "Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)" (12-01-2009)                                           |   |  |
|                                 | 12       | Information from ClinicalTrials.gov archive on the view of NCT00789477 "DME and VEGF Trap-Eye: Investigation of Clinical Impact" (11-18-2010)                                                                                                                          |   |  |
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|                                 | 19       | PAI et al., "Current concepts in intravitreal drug therapy for diabetic retinopathy" Saudi Journal of Ophthalmology 24(4):143-149 (June 30, 2010)                                                                                                                      |   |  |
|                                 | 20       | Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007                                                                                                                                                        |   |  |

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| Examiner Signature |  | Date Considered |  |
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|                                 | 21       | Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008.                                                                                                                                                   |   |  |
|                                 | 22       | Regeneron Press Release "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration" November 22, 2010                                                                              |   |  |
|                                 | 23       | Regeneron Press Release "Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)" December 20, 2010                                        |   |  |
|                                 | 24       | Simo and Hernandez, "Advances in Medical Treatment of Diabetic Retinopathy" Diabetes Care, Volume 32, Number 8, August 2009                                                                                                                                     |   |  |
|                                 | 25       | Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008.                                                                                                                          |   |  |
|                                 | 26       | STEWART, "The expanding role of vascular endothelial growth factor inhibitors in ophthalmology" Mayo Clin Proc. 87(1):77-88 (January 2012)                                                                                                                      |   |  |
|                                 | 27       | THOMAS REUTERS INTEGRITY "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (September 28, 2008)                                                                                               |   |  |
|                                 | 28       | WHO Drug Information, "International Nonproprietary Names for Pharmaceutical Substances (INN)" Vol. 20, No. 2, 2006, pages 115-119.                                                                                                                             |   |  |

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| Examiner Signature | /JON M LOCKARD/ | Date Considered | 03/29/2018 |
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|----------------------------------------------------------------------------------------------------------|--------------------------------------------|--------------------------------------------------------------------------|
| <b>Search Notes</b><br> | <b>Application/Control No.</b><br>15471506 | <b>Applicant(s)/Patent Under Reexamination</b><br>YANCOPOULOS, GEORGE D. |
|                                                                                                          | <b>Examiner</b><br>JON M LOCKARD           | <b>Art Unit</b><br>1647                                                  |

| CPC- SEARCHED |      |          |
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| CPC COMBINATION SETS - SEARCHED |      |          |
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| US CLASSIFICATION SEARCHED |          |           |          |
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| Class                      | Subclass | Date      | Examiner |
| NONE                       |          | 3/29/2018 | JML      |

\* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| SEARCH NOTES                                                           |           |          |
|------------------------------------------------------------------------|-----------|----------|
| Search Notes                                                           | Date      | Examiner |
| STIC Search of SEQ ID NO:2. See search results in SCORE.               | 3/29/2018 | JML      |
| EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.     | 3/29/2018 | JML      |
| STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history. | 3/29/2018 | JML      |
| PALM: Inventor search.                                                 | 3/29/2018 | JML      |

| INTERFERENCE SEARCH     |                         |      |          |
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| L1    | 6537 | (flt1 or vegfr1 or (vegf adj r1)) same ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3))) | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |
| L2    | 1645 | L1 and ((chimer\$ or fusion) same vegf)                                                                             | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |
| L3    | 637  | L1 same ((chimer\$ or fusion) same vegf)                                                                            | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |
| L4    | 6386 | (flt1 or vegfr1 or (vegf adj r1)) with ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3))) | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |
| L5    | 329  | L4 with ((chimer\$ or fusion) with vegf)                                                                            | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |
| L6    | 2004 | (L4 or L5) and ((eye or ocular or retina\$ or macular) with disorder)                                               | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |
| L7    | 274  | (L3 or L5) and ((eye or ocular or retina\$ or macular) with disorder)                                               | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |
| L8    | 14   | (L3 or L5) same ((eye or ocular or retina\$ or macular) with disorder)                                              | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |
| L9    | 422  | yancopoulos-g\$.in.                                                                                                 | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |
| L10   | 44   | L7 and L9                                                                                                           | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |
| L11   | 13   | L10 and (eye ocular macular).clm.                                                                                   | US-PGPUB; USPAT; EPO; DERWENT | OR               | ON      | 2018/03/29 18:42 |

**3/ 29/ 2018 6:43:13 PM****C:\Users\jlockard\Documents\EAST\Workspaces\15471506.wsp**

|                                                          |   |    |   |                        |                         |
|----------------------------------------------------------|---|----|---|------------------------|-------------------------|
| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b> |   |    |   | Application Number     | 15/471,506              |
|                                                          |   |    |   | Filing Date            | March 28, 2017          |
|                                                          |   |    |   | First Named Inventor   | YANCOPOULOS, GEORGE D.  |
|                                                          |   |    |   | Art Unit               | 1647                    |
|                                                          |   |    |   | Examiner Name          | LOCKARD, JON MCCLELLAND |
| Sheet                                                    | 1 | of | 1 | Attorney Docket Number | REGN-008CIPCON2         |

| U.S. PATENT DOCUMENTS |          |                             |                          |                                                    |                                                                                 |
|-----------------------|----------|-----------------------------|--------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|
| Examiner Initial*     | Cite No. | Patent Number               | Issue Date<br>YYYY-MM-DD | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines, Where<br>Relevant Passages or Relevant<br>Figures Appear |
|                       |          | Number-Kind Code (if known) |                          |                                                    |                                                                                 |
|                       | 1        |                             |                          |                                                    |                                                                                 |

| U.S. PATENT APPLICATION PUBLICATIONS |          |                             |                                |                                                    |                                                                                 |
|--------------------------------------|----------|-----------------------------|--------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|
| Examiner Initial*                    | Cite No. | Publication Number          | Publication Date<br>YYYY-MM-DD | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines, Where<br>Relevant Passages or Relevant<br>Figures Appear |
|                                      |          | Number-Kind Code (if known) |                                |                                                    |                                                                                 |
|                                      | 1        |                             |                                |                                                    |                                                                                 |

| FOREIGN PATENT DOCUMENTS |          |                                          |                                |                                                    |                                                                                 |   |
|--------------------------|----------|------------------------------------------|--------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------|---|
| Examiner Initial*        | Cite No. | Foreign Document Number                  | Publication Date<br>YYYY-MM-DD | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines, Where<br>Relevant Passages or Relevant<br>Figures Appear | T |
|                          |          | Country Code-Number-Kind Code (if known) |                                |                                                    |                                                                                 |   |
|                          | 1        |                                          |                                |                                                    |                                                                                 |   |

| NON PATENT LITERATURE DOCUMENTS |          |                                                                                                                                                                                                                                                                 |   |
|---------------------------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|
| Examiner Initials*              | Cite No. | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T |
| /J.L./                          | 1        | MITRA et al., "Review of anti-vascular endothelial growth factor therapy in macular edema secondary to central retinal vein occlusions" Expert Review in Ophthalmology, Taylor & Francis, GB (January 1, 2011) 6(6):623-629                                     |   |
| /J.L./                          | 2        | OLIVERA et al., "VEGF Trap R1R2 suppresses experimental corneal angiogenesis" European Journal of Ophthalmology (January 1, 2010) 20(1):48-54                                                                                                                   |   |
| /J.L./                          | 3        | Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting" (September 28, 2008) (XP-002770952)                                                                          |   |

|                    |                 |                 |            |
|--------------------|-----------------|-----------------|------------|
| Examiner Signature | /JON M LOCKARD/ | Date Considered | 03/29/2018 |
|--------------------|-----------------|-----------------|------------|

EXAMINER: Initial if reference considered; whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**Electronically Filed**

|                                                                                                                                                       |                      |                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|----------------------------|
| <b>AMENDMENT UNDER<br/>37 C.F.R. §1.111</b><br><br>Address to:<br>Mail Stop<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, VA 22313-1450 | Attorney Docket No.  | REGN-008CIPCON2            |
|                                                                                                                                                       | Confirmation No.     | 8014                       |
|                                                                                                                                                       | First Named Inventor | YANCOPOULOS, GEORGE D.     |
|                                                                                                                                                       | Application Number   | 15/471,506                 |
|                                                                                                                                                       | Filing Date          | March 28, 2017             |
|                                                                                                                                                       | Group Art Unit       | 1647                       |
|                                                                                                                                                       | Examiner Name        | LOCKARD, JON<br>MCCLELLAND |
| Title: <i>“Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders”</i>                                                                            |                      |                            |

Sir:

This amendment is responsive to the Office Action dated April 3, 2017 for which a three-month period for response was given making this response timely filed on or before July 3, 2018.

**Amendments to the Specification** begin on page 2 of this document

**Amendments to the Claims** begin on page 3 of this document.

**Remarks/Arguments** begin on page 7 of this document.

**AMENDMENTS TO THE SPECIFICATION**

Please amend paragraph [0001] on page1 of the specification to read as follows:

**[0001]** This application is a continuation of U.S. Patent Application Serial No. 14/972,560, filed December 17, 2015 (~~now allowed~~), **now U.S. Patent No. 9,669,069 issued June 6, 2017** which is a continuation of U.S. Patent Application Serial No. 13/940,370 filed July 12, 2013, now U.S. Patent No. 9,254,338 issued February 9, 2016 which is a continuation-in-part of International Patent Application No. PCT/US2012/020855, filed on January 11, 2012, which claims the benefit of US Provisional Application Nos. 61/432,245, filed on January 13, 2011, 61/434,836, filed on January 21, 2011, and 61/561,957, filed on November 21, 2011, the contents of which are hereby incorporated by reference in their entireties.

**AMENDMENTS TO THE CLAIMS:**

1. - 20. (Canceled)

21. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2;

wherein exclusion criteria for the patient include all of:

- (1) active intraocular inflammation;
- (2) active ocular or periocular infection;
- (3) any ocular or periocular infection within the last 2 weeks prior to treatment.

22. (Previously Presented) The method of claim 21, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

23. (Previously Presented) The method of claim 21, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

24. (Previously Presented) The method of claim 23, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

25. (Previously Presented) The method of claim 21, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

26. (Previously Presented) The method of claim 21, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

27. (Previously Presented) The method of claim 26, wherein the angiogenic eye disorder is age related macular degeneration.

28. (Previously Presented) The method of claim 21, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

29. (Previously Presented) The method of claim 28, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

30. (Previously Presented) The method of claim 29, wherein the intraocular administration is intravitreal administration.

31. (Previously Presented) The method of claim 30, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

32. (Previously Presented) The method of claim 31, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

33. (Previously Presented) The method of claim 31, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

34. (Previously Presented) A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist,

followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose;  
and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1;

wherein exclusion criteria for the patient include all of:

- (1) active intraocular inflammation;
- (2) active ocular or periocular infection;
- (3) any ocular or periocular infection within the last 2 weeks prior to treatment.

35. (Previously Presented) The method of claim 34, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks after the initial dose of the VEGF antagonist.

36. (Previously Presented) The method of claim 34, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

37. (Previously Presented) The method of claim 36, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose.

38. (Previously Presented) The method of claim 37, wherein the angiogenic eye disorder is age related macular degeneration.

39. (Previously Presented) The method of claim 34, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose.

40. (Previously Presented) The method of claim 34, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

41. (Previously Presented) The method of claim 34, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

42. (Previously Presented) The method of claim 41, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

43. (Previously Presented) The method of claim 41, wherein the intraocular administration is intravitreal administration.

44. (Previously Presented) The method of claim 43, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

45. (Previously Presented) The method of claim 44, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

46. (Previously Presented) The method of claim 44, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

**REMARKS**

**FORMAL MATTERS:**

Claims 21-46 are now pending in this application.

Claims 1-20 were previously canceled without prejudice.

No claims are amended or added.

No new matter is added.

**DOUBLE PATENTING REJECTIONS – ‘338 PATENT**

Claims 21-46 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-26 of issued U.S. Patent 9,254,338 and claims 1-12 of U.S. Patent 9,669,069.

Without acquiescing to the validity of the rejection, applicants have attached a terminal disclaimer which is specific to U.S. Patent 9,254,338 and 9,669,069 thereby rendering the rejection moot.

**DOUBLE PATENTING REJECTIONS – ‘746; ‘747; ‘799; AND ‘049 PATENTS**

There are four additional obviousness type double patenting rejections.

In section 8 of the Office Action, claims 21-46 are rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-5 of issued U.S. Patent 7,303,746.

In section 9 of the Office Action, claims 21-46 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-6 of issued U.S. Patent 7,303,747.

In section 10 of the Office Action, claims 21-46 were rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-11 of issued U.S. Patent 7,306,799.

In section 11 of the Office Action, claims 21-46 were rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-15 of issued U.S. Patent 7,521,049.

The rejections in sections 8, 9, 10 and 11 are traversed for the reasons indicated below and as further supported by the attached publication.

**NON-OBVIOUSNESS RESPONSE**

None of the ‘746, ‘747, ‘799 or ‘049 patents disclose the treatment protocol of the pending claims. Thus, based on the working examples set forth in the present application, along with the

endorsement of the present invention as set out in the attached (Heier et al.) peer reviewed publication, as well as the facts and reasoning provided below, the rejection should be reconsidered and withdrawn.

At the time of the invention the well accepted standard of care for the treatment of the neovascular (or wet) form of age-related macular degeneration (AMD) was to administer an antibody formulation (ranibizumab) by injection to the eye once per month (see the attached Heier et al. paper).

This treatment protocol is (1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the patient to potential adverse effects such as infection with each treatment event.

Due to all the above factors (1-5) there was a need in the art for alternative treatment protocols whereby the treatment would be carried out with less inconvenience and reduced safety risks to the patient. However, until the present invention once a month treatment remained the standard of care.

There are virtually an infinite number of different treatment protocols that could be tested. A drug could be administered more frequently, or less frequently, relative to the accepted standard of care. Further, different variations in timing between dosing events are possible. Due to the virtually infinite number of combinations, applicants do not believe that the claimed treatment protocol is *prima facie* obvious in view of the prior art standard of care which is administration of the drug once per month. However, notwithstanding that position, any *prima facie* case of obviousness is overcome by the showing of improved unexpected results. Thus, while the rejection is citing case law (In re Aller) which supports the position that where the general conditions of a claim are disclosed within the prior art, it is not inventive to discover optimal ranges, the Examiner is aware that this case law is not applicable to situations where improved unexpected results are shown (MPEP 2145). Such results have been obtained and are described in the working examples of the present application and in the attached (Heier et al.) publication, portions of which are referred to below.

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

The attached Heier et al. paper published in December of 2012, and as such is not prior art with respect to the present application filed on January 11, 2012 and claiming priority to November 21, 2011.

The Heier et al. paper shows results of a treatment protocol of the type claimed on over 2,400 patients. The studies summarized in the Heier *et al.* paper correspond to the clinical trials disclosed in Example 4 of the present application which involve the use of the VEGF receptor-based chimeric molecule known as aflibercept or "VEGF Trap."<sup>1</sup> The results clearly show that by administering the specifically claimed VEGF antagonist in accordance with a dosage regimen as claimed in independent claim 1, it is possible to treat angiogenic eye disorders such as AMD while administering doses on a less frequent basis than previously thought possible. This (1) provides enormous benefits to patients, (2) reduces health care cost, (3) reduces the pain and (4) suffering of the patient, as well as (5) the inconvenience to the patient and their family, and as such provides a major step forward in the treatment of patients suffering from angiogenic eye disorders, which is worthy of patent protection.

The attached Heier et al. article is a peer reviewed article published in "Ophthalmology" which describes the aforementioned clinical trial as follows:

"Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every 4 weeks (0.5q4); 2 mg aflibercept every 4 weeks (2q4); 2mg aflibercept every 8 weeks (2q8) after 3 injections at week 0, 4 and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or 0.5mg ranibizumab every 4 weeks (Rq4). Consecutively enrolled patients were assigned to treatment groups on the basis of predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system. "

In the "primary end point analysis" section of the paper, it is indicated that the proportion of patients maintaining vision was similar among all treatment groups and this is dramatically shown within Table 2 of Heier et al. Thus, the results show that the treatment groups which were compared with the monthly treatment groups surprisingly did not obtain an inferior result. As such, the PRN treatment protocol as encompassed by the presently pending independent claim 21 and 34 achieves results which are as good or better than the results obtained with monthly treatment.

Within the "Discussion" section of the Heier et al. paper, it is noted that the treatment group treated every two months achieved a visual acuity score within 0.3 letters of the group treated on a

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<sup>1</sup> Aflibercept is a VEGF receptor-based chimeric molecule as defined in the claims and specifically in claims 21 and 34.

monthly basis. See also the results summarized in Table 1, page 15, of the present application. Thus, it is indicated that the treatment group which received the drug far less frequently than the monthly dosing arm achieved remarkably similar improvements without requiring the monthly monitoring and visits to the health care provider.

Similar remarkable results are shown in Example 5 of the present application, which illustrates an administration regimen encompassed by claims 21 and 34 (*i.e.*, 3 initial doses of VEGF Trap administered once every four weeks, followed by additional doses administered as needed (PRN)) for the effective treatment of diabetic macular edema (DME). As noted at paragraph [0065] of the present specification: "the administration of VEGFT to patients suffering from angiogenic eye disorders (*e.g.*, AMD and DME) at a frequency of once every 8 weeks, following a single initial dose and two secondary doses administered four weeks apart, resulted in significant prevention of moderate or severe vision loss or improvements in visual acuity."

An acknowledgement of the unexpected results of the administration regimen of the present invention is echoed in the Heier et al. paper, which points out that less frequent injections should also provide an ocular safety benefit, and that using fewer injections may substantially decrease the cumulative population risk of certain adverse events which can have a considerable impact considering the millions of injections given each year. For example, Heier et al. states on page 2546, middle left column that:

"The demonstration that monthly aflibercept provides similar efficacy and safety as the current approved standard of monthly ranibizumab is important, but the finding that remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians."

Moreover, the final paragraph of the Heier et al. paper reads as follows:

"In conclusion, intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as similar safety and tolerability. Intravitreal aflibercept dosed every 2 months has the potential to provide patients, their families and clinicians the

opportunity for the optimal vision gains and anatomic disease control they have come to expect from monthly ranibizumab, with a substantially decreased treatment and compliance burden, and a lower cumulative risk of injection-related adverse events.”

Based on the above, it is clear that the claimed treatment protocol provides enormous advantages to patients. Further, in view of the disadvantages of carrying out the treatment on a once per month basis, there was a need in the art for alternative treatment protocols. However, this did not occur until the present invention and as such, the claimed treatment protocol is inventive above and beyond the inventions claimed within the patents cited in the obviousness type double patenting rejection. In view of such, those rejections should be reconsidered and withdrawn.

**STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2**

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant’s duty to disclose under 37 C.F.R. §§1.56 and 1.2 ( see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner’s attention that U.S. Patent Application 14/972,560, filed December 16, 2015 which issued on June 6, 2017 as U.S. Patent No. 9,669,069.

The Applicants wish to bring to the Examiner’s attention that U.S. Patent Application 13/940,370, filed July 12, 2013 which issued on February 9, 2016 as U.S. Patent No. 9,254,338.

The Applicants wish to bring to the Examiner’s attention that U.S. Patent Application 10/988,243, filed November 12, 2004 which issued on December 4, 2007 as U.S. Patent No. 7,303,746.

The Applicants wish to bring to the Examiner’s attention that U.S. Patent Application 11/218,234, filed September 1, 2005 which issued on December 4, 2007 as U.S. Patent No. 7,303,747.

The Applicants wish to bring to the Examiner’s attention that U.S. Patent Application 11/089,803, filed March 25, 2005 which issued on December 11, 2007 as U.S. Patent No. 7,306,799.

The Applicants wish to bring to the Examiner’s attention that U.S. Patent Application 11/998,709, filed November 30, 2007 which issued on April 21, 2009 as U.S. Patent No. 7,521,049.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

**CONCLUSION**

Applicants do not acquiesce to the *prima facie* obviousness of the claimed invention over the invention claimed within the cited patents. This is because there are virtually an infinite number of different possible treatment protocols. However, notwithstanding any *prima facie* case of obviousness, applicants have demonstrated improved and unexpected results, and based on such, the rejections should be reconsidered and withdrawn.

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of \$3,000.00 beyond that authorized on the credit card, but not more than \$3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-008CIPCON2.

Respectfully submitted,  
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 25, 2018

By: /Karl Bozicevic, Reg. No. 28,807/  
Karl Bozicevic, Reg. No. 28,807

Enclosures: (1) Heier et al.

(2) Terminal Disclaimer regarding U.S. Patent Nos. 9,254,338 and 9,669,069

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| Electronic Patent Application Fee Transmittal        |                 |                                                            |               |                             |
|------------------------------------------------------|-----------------|------------------------------------------------------------|---------------|-----------------------------|
| <b>Application Number:</b>                           |                 | 15471506                                                   |               |                             |
| <b>Filing Date:</b>                                  |                 | 28-Mar-2017                                                |               |                             |
| <b>Title of Invention:</b>                           |                 | USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS |               |                             |
| <b>First Named Inventor/Applicant Name:</b>          |                 | George D. YANCOPOULOS                                      |               |                             |
| <b>Filer:</b>                                        |                 | Karl Bozicevic/Savanna Fuentes                             |               |                             |
| <b>Attorney Docket Number:</b>                       |                 | REGN-008CIPCON2                                            |               |                             |
| Filed as Large Entity                                |                 |                                                            |               |                             |
| <b>Filing Fees for   Utility under 35 USC 111(a)</b> |                 |                                                            |               |                             |
| <b>Description</b>                                   | <b>Fee Code</b> | <b>Quantity</b>                                            | <b>Amount</b> | <b>Sub-Total in USD(\$)</b> |
| <b>Basic Filing:</b>                                 |                 |                                                            |               |                             |
| <b>Pages:</b>                                        |                 |                                                            |               |                             |
| <b>Claims:</b>                                       |                 |                                                            |               |                             |
| <b>Miscellaneous-Filing:</b>                         |                 |                                                            |               |                             |
| <b>Petition:</b>                                     |                 |                                                            |               |                             |
| <b>Patent-Appeals-and-Interference:</b>              |                 |                                                            |               |                             |
| <b>Post-Allowance-and-Post-Issuance:</b>             |                 |                                                            |               |                             |
| <b>Extension-of-Time:</b>                            |                 |                                                            |               |                             |

| Description                      | Fee Code | Quantity | Amount | Sub-Total in USD(\$) |
|----------------------------------|----------|----------|--------|----------------------|
| <b>Miscellaneous:</b>            |          |          |        |                      |
| STATUTORY OR TERMINAL DISCLAIMER | 1814     | 1        | 160    | 160                  |
| <b>Total in USD (\$)</b>         |          |          |        | <b>160</b>           |

## Electronic Acknowledgement Receipt

|                                             |                                                            |
|---------------------------------------------|------------------------------------------------------------|
| <b>EFS ID:</b>                              | 32990996                                                   |
| <b>Application Number:</b>                  | 15471506                                                   |
| <b>International Application Number:</b>    |                                                            |
| <b>Confirmation Number:</b>                 | 8014                                                       |
| <b>Title of Invention:</b>                  | USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS |
| <b>First Named Inventor/Applicant Name:</b> | George D. YANCOPOULOS                                      |
| <b>Customer Number:</b>                     | 96387                                                      |
| <b>Filer:</b>                               | Karl Bozicevic/Savanna Fuentes                             |
| <b>Filer Authorized By:</b>                 | Karl Bozicevic                                             |
| <b>Attorney Docket Number:</b>              | REGN-008CIPCON2                                            |
| <b>Receipt Date:</b>                        | 25-JUN-2018                                                |
| <b>Filing Date:</b>                         | 28-MAR-2017                                                |
| <b>Time Stamp:</b>                          | 15:48:58                                                   |
| <b>Application Type:</b>                    | Utility under 35 USC 111(a)                                |

### Payment information:

|                                                                                                                |                       |
|----------------------------------------------------------------------------------------------------------------|-----------------------|
| Submitted with Payment                                                                                         | yes                   |
| Payment Type                                                                                                   | CARD                  |
| Payment was successfully received in RAM                                                                       | \$ 160                |
| RAM confirmation Number                                                                                        | 062618INTEFSW15493700 |
| Deposit Account                                                                                                |                       |
| Authorized User                                                                                                |                       |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: |                       |

|                              |                                                       |                                                    |                                           |                  |                  |
|------------------------------|-------------------------------------------------------|----------------------------------------------------|-------------------------------------------|------------------|------------------|
|                              |                                                       |                                                    |                                           |                  |                  |
| File Listing:                |                                                       |                                                    |                                           |                  |                  |
| Document Number              | Document Description                                  | File Name                                          | File Size(Bytes)/ Message Digest          | Multi Part /.zip | Pages (if appl.) |
| 1                            | Non Patent Literature                                 | Heier_2012.pdf                                     | 714624                                    | no               | 12               |
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| 3                            |                                                       | REGN-008CIPCON2_2018-06-25_amend.pdf               | 98613                                     | yes              | 12               |
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| 4                            | Fee Worksheet (SB06)                                  | fee-info.pdf                                       | 30325                                     | no               | 2                |
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# Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration

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**Objective:** Two similarly designed, phase-3 studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) of neovascular age-related macular degeneration (AMD) compared monthly and every-2-month dosing of intravitreal aflibercept injection (VEGF Trap-Eye; Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) with monthly ranibizumab.

**Design:** Double-masked, multicenter, parallel-group, active-controlled, randomized trials.

**Participants:** Patients (n = 2419) with active, subfoveal, choroidal neovascularization (CNV) lesions (or juxtafoveal lesions with leakage affecting the fovea) secondary to AMD.

**Intervention:** Patients were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every 2 months after 3 initial monthly doses (2q8), or ranibizumab 0.5 mg monthly (Rq4).

**Main Outcome Measures:** The primary end point was noninferiority (margin of 10%) of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart). Other key end points included change in best-corrected visual acuity (BCVA) and anatomic measures.

**Results:** All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab for the primary end point (the 2q4, 0.5q4, and 2q8 regimens were 95.1%, 95.9%, and 95.1%, respectively, for VIEW 1, and 95.6%, 96.3%, and 95.6%, respectively, for VIEW 2, whereas monthly ranibizumab was 94.4% in both studies). In a prespecified integrated analysis of the 2 studies, all aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA; all aflibercept regimens also produced similar improvements in anatomic measures. Ocular and systemic adverse events were similar across treatment groups.

**Conclusions:** Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab. These studies demonstrate that aflibercept is an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.

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\*Group members listed online in Appendix 1 (<http://aaojournal.org>).

Age-related macular degeneration (AMD) is a leading cause of vision loss and blindness in industrialized countries.<sup>1</sup> The most severe vision loss occurs in the neovascular (or wet) form of AMD, involving choroidal neovascularization (CNV) and associated retinal edema. Early treatments for CNV (laser ablation, photodynamic therapy with verteporfin), although clearly better than no treatment at all, decreased severe vision loss rather than truly stabilizing vision or resulting in clinically significant improvements in visual acuity.<sup>2–4</sup> The suggestion that vascular endothelial growth factor (VEGF) might be driving the CNV and associated edema seen in AMD led to a paradigm shift with the success of the first anti-VEGF therapy, pegaptanib sodium.<sup>5,6</sup> Monthly intravit-

real injections of 0.5 mg ranibizumab, a humanized monoclonal antibody fragment that blocks VEGF, not only prevent vision loss in most patients but also lead to significant visual gain in approximately one-third.<sup>7,8</sup> The risk of rare but serious adverse events resulting from the intravitreal procedure, together with the significant burden of making monthly visits to their retinal specialist, have led to extensive efforts to decrease injection and monitoring frequency. However, fixed quarterly<sup>9,10</sup> or “as needed” (pro re nata [PRN]) dosing regimens,<sup>11,12</sup> without requiring monthly monitoring visits, were not effective at maintaining vision.

The Comparison of AMD Treatments Trials (CATT)<sup>13</sup> recently compared monthly ranibizumab with monthly

bevacizumab, as well as with PRN regimens that required monthly monitoring visits during which treatment decisions primarily were made on the basis of anatomic criteria. Monthly bevacizumab resulted in mean best-corrected visual acuity (BCVA) gains (8.0 letters) similar to those for monthly ranibizumab (8.5 letters), whereas PRN ranibizumab yielded a mean BCVA gain of 1.7 letters less than that of the monthly standard (with a confidence interval [CI] extending to 4.7 letters below) that achieved noninferiority, and PRN bevacizumab yielded a mean BCVA gain 2.6 letters below the monthly standard (with a CI extending to 5.9 letters below) that did not achieve noninferiority. In the CATT, monthly bevacizumab and both PRN regimens were significantly worse than monthly ranibizumab in terms of the propor-

tion of patients who had fluid-free retinas on optical coherence tomography (OCT). Although CIs were not provided for monthly and PRN regimens, switching from monthly to PRN regimens in the second year of the CATT resulted in a significant worsening of BCVA and retinal thickness, as well as a significant decrease in the proportion of patients without retinal fluid.<sup>14</sup> The “alternative treatments to Inhibit VEGF in Age-related chorioidal Neovascularization” (IVAN) study also found that the mean foveal retinal thickness and the percentage of patients with fluorescein leakage were significantly higher with the PRN regimen compared with the monthly regimen.<sup>15</sup> In the HARBOR study (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677), PRN regimens of both the approved 0.5 mg dose and the higher 2 mg dose of

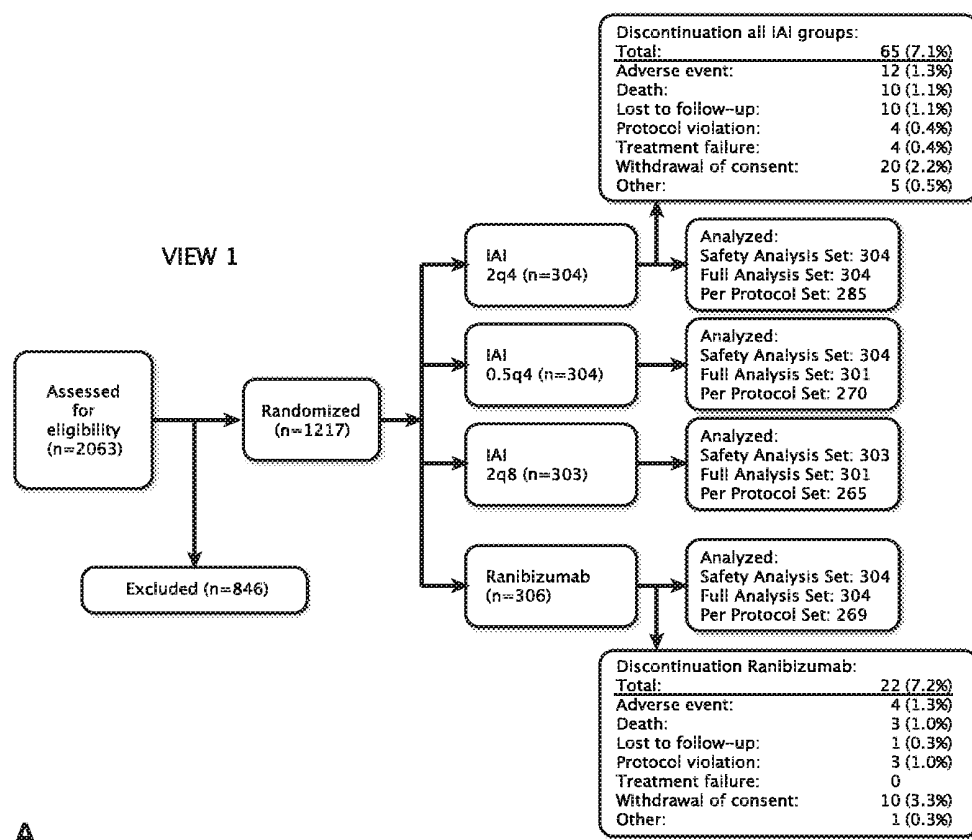


**Figure 1.** Flowcharts describing treatment allocation and patient disposition in VIEW 1 (A) and VIEW 2 (B). In both VIEW 1 and VIEW 2 studies, the most common reason for patients to be screened but not randomized was ineligibility based on angiographic characteristics as identified by the reading center. The second most common reason was visual acuity out of range. Discontinuations are those that occurred from the study. Two milligrams intravitreal aflibercept every 2 months (2q8) dosing was performed after 3 initial monthly doses. The numbers of patients who prematurely discontinued study medication in the 2q4, 0.5q4, 2q8, and Rq4 groups were 16 (5.3%), 30 (9.9%), 30 (9.9%), and 27 (8.8%), respectively, in VIEW 1; and 37 (11.8%), 45 (14.5%), 33 (10.5%), and 33 (10.9%), respectively, in VIEW 2. In VIEW 1, 1089 patients were included in the per protocol set (PPS), with 92.6% to 96.1% completing week-52 visual acuity assessment. A total of 128 patients were not included in the PPS for the following reasons (in order of occurrence): missed 2 consecutive injections before ninth injection, major protocol deviation, received <9 injections, had <9 assessments, no baseline assessments, no post-baseline assessments. In VIEW 2, 1081 patients were included in the PPS with 95.9% to 97.8% completing week-52 visual acuity assessment. A total of 159 patients were not included in the PPS for the following main reasons: missed 2 consecutive injections before ninth injection, major protocol deviation, received <9 injections, had <9 assessments, no baseline assessments, no post-baseline assessments, unmasking by investigator or Global Pharmacovigilance. 0.5q4 = 0.5 mg IAI monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses; IAI = intravitreal aflibercept injection.

ranibizumab did not achieve noninferiority compared with monthly ranibizumab, with the 0.5 mg PRN regimen yielding a mean BCVA gain 2.0 letters below the monthly standard (with a CI extending to 4.5 letters below). Of note, just like the CATT PRN regimens, the HARBOR PRN regimens still depended on monthly monitoring visits. Thus, there remains a need for new therapies that will provide equivalent efficacy and anatomic disease control to monthly ranibizumab, while reducing the risk of monthly injections and the burden of mandatory monthly monitoring visits.

Intravitreal aflibercept injection (IAI) (previously known in the scientific literature as VEGF Trap-Eye, Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) is a soluble decoy receptor fusion protein<sup>16,17</sup> that is specifically purified and formulated for intraocular injection. Intravitreal aflibercept at doses of 0.5 mg and 2 mg provided the most robust outcomes in the Clinical Evaluation of Antiangiogenesis in the Retina Intravitreal Trial Phase 2 (CLEAR-IT 2) study after 4 monthly administrations followed by PRN dosing to week 52.<sup>18</sup> The binding affinity of intravitreal aflibercept to VEGF is substantially greater than that of bevacizumab or ranibizumab.<sup>17</sup> The greater affinity could translate into a higher efficacy or, as predicted by a mathematic model, into a substantially longer duration of

action in the eye,<sup>19</sup> allowing for less frequent dosing, as supported by early clinical trials.<sup>18,20</sup> In this article, we report the first-year results of 2 phase 3 studies comparing intravitreal aflibercept, monthly or every 2 months, with monthly ranibizumab.

## Materials and Methods

### Study Design

The “VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD” studies (VIEW 1 and VIEW 2) were similarly designed, prospective, double-masked, multinational, parallel-group, active-controlled, randomized clinical trials. The investigators from the VIEW 1 and VIEW 2 studies are listed in Appendix 1, available at <http://aaojournal.org>. Patients in VIEW 1 (registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) on July 31, 2007; NCT00509795. Accessed August 8, 2012) were randomized at 154 sites in the United States and Canada. Patients in VIEW 2 (registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) on March 12, 2008; NCT00637377. Accessed August 8, 2012) were randomized at 172 sites in Europe, the Middle East, Asia-Pacific, and Latin America; the last patient in both studies completed 52 weeks in September 2010. The study protocols were approved by institutional review boards or ethics committees for each clinical site; all participants provided written informed consent. All the US study sites complied with the Health Insurance

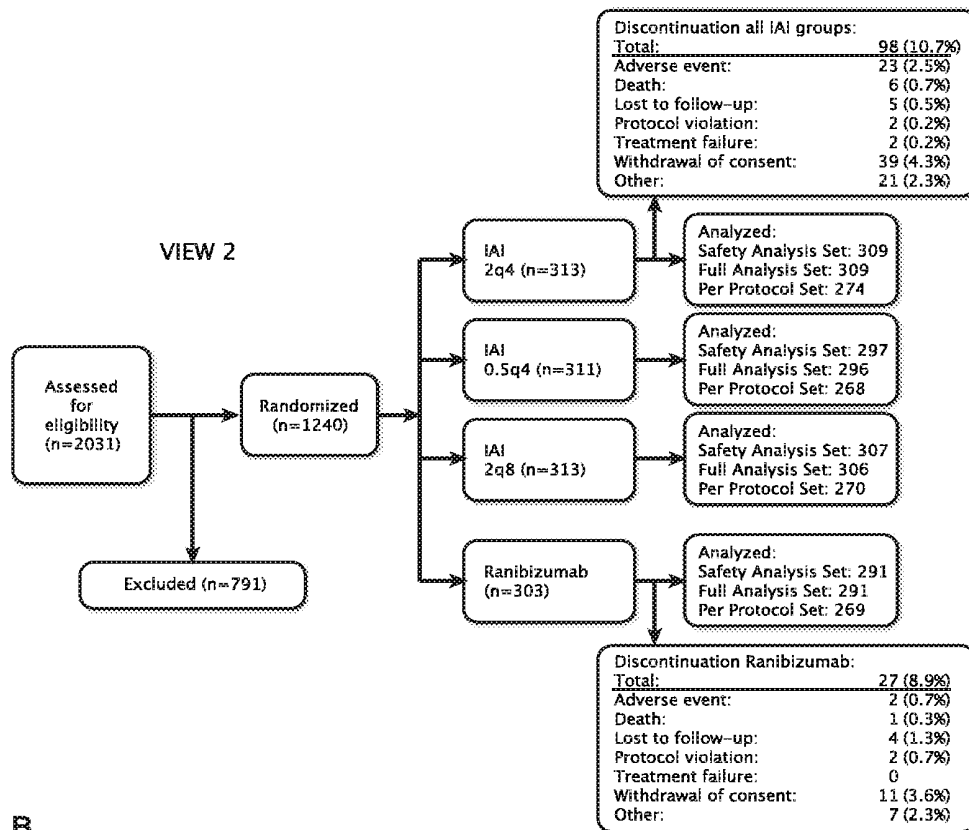


Figure 1. (Continued.)

Portability and Accountability Act. The 52-week outcomes are reported.

## Participants

Inclusion and exclusion criteria were designed to maintain constancy with the pivotal trials for the reference drug ranibizumab, consistent with regulatory guidelines for noninferiority studies, and included (1) age  $\geq 50$  years with active subfoveal CNV lesions (any subtype) secondary to AMD; juxtafoveal lesions with leakage affecting the fovea also were allowed; (2) CNV comprising at least 50% of total lesion size; and (3) BCVA between 73 and 25 Early Treatment Diabetic Retinopathy Study chart (ETDRS) letters (20/40–20/320 Snellen equivalent). Patients with prior treatment for AMD (including an investigational agent or anti-VEGF therapy) in the study eye were excluded. Eligibility was determined using fluorescein angiography at the reading center. Complete eligibility criteria are shown in Appendix 2 (available at <http://aaojournal.org>).

## Treatment Groups and Randomization

Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every 4 weeks (0.5q4); 2 mg aflibercept every 4 weeks (2q4); 2 mg aflibercept every 8 weeks (2q8) after 3 injections at week 0, 4, and 8 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or 0.5 mg ranibizumab every 4 weeks (Rq4). Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system.

## End Points and Statistical Analyses

The primary end point analysis, noninferiority margins, and definition of “clinical equivalence” were established in discussion with the Food and Drug Administration (FDA) (as part of a Special Protocol Assessment), European Medicines Agency, Pharmaceutical and Medical Device Agency and other regulatory authorities, with the intent of maintaining constancy with the previous ranibizumab pivotal trials<sup>7,8</sup> and preserving the majority of the treatment effect demonstrated in these trials. The primary end point analysis was noninferiority of the intravitreal aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing  $<15$  ETDRS letters; per protocol data set) in each study. A noninferiority margin of 10% in the individual studies was chosen to preserve approximately two-thirds of the ranibizumab effect for prevention of moderate vision loss (loss of  $<15$  letters) demonstrated in pivotal ranibizumab studies,<sup>7,8</sup> using the 2 CI approach. The FDA suggested that a margin of 5% could determine clinical equivalence. Thus, the margin of 10% was used for assessing noninferiority, and the margin of 5% was used for assessing clinical equivalence. The prespecified analysis plan also included a prospectively planned integrated analysis combining the 2 VIEW studies; in this integrated analysis, the European Medicines Agency/Committee for Medicinal Products for Human Use requested a noninferiority margin of 7%. In the individual studies, the primary end point was assessed by a prespecified hierarchical testing sequence of noninferiority to ranibizumab with the sequence of aflibercept 2q4, 0.5q4, and then 2q8 to control the 5% (4.9% for VIEW 1) overall type I error while maintaining a 5% significance level (4.9% for

VIEW 1) for each individual comparison (see Appendices 3 and 4 for details of the statistical analysis, available at <http://aaojournal.org>). If all aflibercept groups demonstrated noninferiority to ranibizumab for the primary end point, additional comparisons with ranibizumab were prespecified regarding the secondary end points, also using a hierarchical testing sequence in which each secondary end point was tested for superiority of aflibercept over ranibizumab. Prespecified secondary efficacy variables compared baseline and 52-week data regarding mean change in BCVA; gaining  $\geq 15$  letters; change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) score; and change in CNV area on fluorescein angiography. Anatomic measures included retinal thickness and persistent fluid as assessed by OCT. Change in BCVA also was assessed as part of the prospectively planned prespecified integrated analysis combining the 2 studies.

The full analysis set included all randomized patients who received any study medication and had a baseline and at least 1 post-baseline BCVA assessment. The per protocol set (PPS) included all patients in the full analysis set who (1) received at least 9 doses of study drug and attended at least 9 scheduled visits during the first year, (2) had not missed 2 consecutive injections before administration of the ninth injection (per patient), and (3) did not have major protocol violations. Sham injections were counted as doses administered for the purpose of defining the PPS. The PPS included patients who discontinued the study because of treatment failure, without a major protocol deviation, at any time during the first 52 weeks (even if they met points 1 and 2 above). These patients were considered nonresponders for the primary end-point analysis. The last observation carried forward (LOCF) approach was used to impute missing values. When indicated, the robustness of analysis results was assessed by using the observed case or completers' data. A completer was defined as a patient who received treatment for at least 9 months and had efficacy data for at least 9 months during the 52 weeks of study. The missing values for completers also were imputed using the LOCF approach.

## Schedule of Visits and Assessments

Patients were examined on the day of treatment initiation and every 4 weeks thereafter through 52 weeks, as well as 1 week after first treatment for safety assessment (subsequent safety assessments occurred by telephone). Each 4-week visit included BCVA assessment and anterior/posterior segment examination (with intraocular pressure determination) before injection (active or sham) and posterior segment examination with intraocular pressure determination 30 to 60 minutes after injection. For the 2q8 treatment group, no treatment decisions were made at the interim monthly visits. The NEI VFQ-25 assessment occurred at screening and weeks 12, 24, 36, and 52. Adverse events were recorded at every visit.

## Imaging Assessments

Fundus photography and fluorescein angiography were performed at screening and weeks 24 and 52, and evaluated by an independent center (Digital Angiography Reading Center, New York). Optical coherence tomography was performed using time domain Stratus machines (Carl Zeiss Meditec, Jena, Germany) and evaluated by an independent center (VIEW 1: OCT Reading Center at Duke, Durham, NC; VIEW 2: Vienna Reading Center, Austria). Visual acuity examiners were certified to ensure consistent measurement of BCVA. In VIEW 1, OCT was performed at screening, at the treatment initiation visit, and at weeks 4, 12, 24, 36, and 52

(and was optional at the investigators' discretion at other study visits). In VIEW 2, OCT was performed at every study visit. Areas of visible CNV (classic or occult) were identified when angiographic analyses showed evidence of late leakage or pooling of dye.

## Masking

Patients were masked as to treatments. An unmasked investigator performed the study drug or sham injection. An unmasked investigator also was responsible for the receipt, tracking, preparation, destruction, and administration of study drug, as well as safety assessments both pre- and post-dose. A separate masked physician assessed adverse events and supervised the masked assessment of efficacy. All other study site personnel were masked to treatment assignment by separating study records or masked packaging. Optical coherence tomography technicians and visual acuity examiners remained masked relative to treatment assignment. Intravitreal aflibercept and sham kits were packaged identically. Lucentis (Genentech Inc, South San Francisco, CA) was obtained commercially but only prepared and delivered by unmasked personnel at the sites.

## Results

### Patient Disposition, Baseline Characteristics, and Exposure

The disposition of patients is shown in Figure 1A-B. In VIEW 1, 1217 patients were randomized, with 91.1% to 96.4% of patients completing 52 weeks. In VIEW 2, 1240 patients were randomized, with 88.1% to 91.1% completing 52 weeks. Baseline demographics and disease characteristics were evenly balanced among all treatment groups (Table 1). The mean number of active injections received by patients in all monthly treatment arms, which were scheduled to receive 13 monthly injections, was 12.1 to 12.5 in VIEW 1 and 12.2 to 12.4 in VIEW 2. The aflibercept every-2-month groups, scheduled to receive 3 initial monthly injections followed by 5 active injections over the next 10 months, received an average of 7.5 active injections in VIEW 1 and in VIEW 2.

### Primary End Point Analysis

In both studies, the proportion of patients maintaining vision was similar among all treatment groups in the prespecified per-protocol analysis and the full analysis set (Table 2). All aflibercept groups achieved statistical noninferiority compared with monthly ranibizumab, with the CIs of the difference between ranibizumab and

Table 1. Patient Demographics and Baseline Characteristics

|                                                      | VIEW 1            |                          |                   |                   | VIEW 2            |                          |                   |                   |
|------------------------------------------------------|-------------------|--------------------------|-------------------|-------------------|-------------------|--------------------------|-------------------|-------------------|
|                                                      | Ranibizumab       | Intravitreal Aflibercept |                   |                   | Ranibizumab       | Intravitreal Aflibercept |                   |                   |
|                                                      | 0.5q4             | 2q4                      | 0.5q4             | 2q8               | 0.5q4             | 2q4                      | 0.5q4             | 2q8               |
| N (full analysis set)                                | 304               | 304                      | 301               | 301               | 291               | 309                      | 296               | 306               |
| Age, yrs (mean $\pm$ SD)                             | 78.2 $\pm$ 7.6    | 77.7 $\pm$ 7.9           | 78.4 $\pm$ 8.1    | 77.9 $\pm$ 8.4    | 73.0 $\pm$ 9.0    | 74.1 $\pm$ 8.5           | 74.7 $\pm$ 8.6    | 73.8 $\pm$ 8.6    |
| Race                                                 |                   |                          |                   |                   |                   |                          |                   |                   |
| White                                                | 296 (97.4)        | 295 (97.0)               | 291 (96.7)        | 287 (95.3)        | 213 (73.2)        | 226 (73.1)               | 219 (74.0)        | 217 (70.9)        |
| Black                                                | 1 (0.3)           | 1 (0.3)                  | 0                 | 1 (0.3)           | 1 (0.3)           | 0                        | 1 (0.3)           | 2 (0.7)           |
| Asian                                                | 0                 | 3 (1.0)                  | 5 (1.7)           | 4 (1.3)           | 60 (20.6)         | 67 (21.7)                | 61 (20.6)         | 69 (22.5)         |
| Other                                                | 7 (2.3)           | 5 (1.6)                  | 5 (1.7)           | 9 (3.0)           | 17 (5.8)          | 16 (5.2)                 | 15 (5.1)          | 18 (5.9)          |
| Sex                                                  |                   |                          |                   |                   |                   |                          |                   |                   |
| Men, n (%)                                           | 132 (43.4)        | 110 (36.2)               | 134 (44.5)        | 123 (40.9)        | 122 (41.9)        | 133 (43.0)               | 149 (50.3)        | 131 (42.8)        |
| Women, n (%)                                         | 172 (56.6)        | 194 (63.8)               | 167 (55.5)        | 178 (59.1)        | 169 (58.1)        | 176 (57.0)               | 147 (49.7)        | 175 (57.2)        |
| Baseline ETDRS BCVA (mean $\pm$ SD)                  | 54.0 $\pm$ 13.4   | 55.2 $\pm$ 13.2          | 55.6 $\pm$ 13.1   | 55.7 $\pm$ 12.8   | 53.8 $\pm$ 13.5   | 52.8 $\pm$ 13.9          | 51.6 $\pm$ 14.2   | 51.6 $\pm$ 13.9   |
| Proportion of patients with $\geq$ 20/40 BCVA, % (n) | 4.3% (13)         | 4.9% (15)                | 6.3% (19)         | 6.6% (20)         | 2.7% (8)          | 2.6% (8)                 | 5.4% (16)         | 3.3% (10)         |
| CNV area, mm <sup>2</sup> (mean $\pm$ SD)            | 6.53 $\pm$ 5.2    | 6.59 $\pm$ 5.1           | 6.49 $\pm$ 4.5    | 6.57 $\pm$ 5.1    | 7.59 $\pm$ 5.3    | 8.25 $\pm$ 5.8           | 7.70 $\pm$ 5.3    | 7.75 $\pm$ 5.5    |
| Lesion type                                          |                   |                          |                   |                   |                   |                          |                   |                   |
| Predominantly classic, n (%)                         | 82 (27.0)         | 87 (28.6)                | 81 (26.9)         | 71 (23.6)         | 70 (24.1)         | 72 (23.3)                | 80 (27.0)         | 88 (28.8)         |
| Minimally classic, n (%)                             | 101 (33.2)        | 105 (34.5)               | 97 (32.2)         | 110 (36.5)        | 104 (35.7)        | 112 (36.2)               | 103 (34.8)        | 106 (34.6)        |
| Occult, n (%)                                        | 115 (37.8)        | 110 (36.2)               | 121 (40.2)        | 118 (39.2)        | 116 (39.9)        | 123 (39.8)               | 113 (38.2)        | 110 (35.9)        |
| Patients with juxtafoveal lesions, n (%)             | 15 (4.9)          | 13 (4.3)                 | 17 (5.6)          | 17 (5.6)          | 20 (6.9)          | 15 (4.9)                 | 11 (3.7)          | 14 (4.6)          |
| Lesion size, mm <sup>2</sup> (mean $\pm$ SD)         | 6.99 $\pm$ 5.5    | 6.98 $\pm$ 5.4           | 6.95 $\pm$ 4.7    | 6.89 $\pm$ 5.2    | 8.01 $\pm$ 5.7    | 8.72 $\pm$ 6.1           | 8.17 $\pm$ 5.5    | 8.22 $\pm$ 5.9    |
| Central retinal thickness, $\mu$ m (mean $\pm$ SD)   | 315.3 $\pm$ 108.3 | 313.6 $\pm$ 103.4        | 313.2 $\pm$ 106.0 | 324.4 $\pm$ 111.2 | 325.9 $\pm$ 110.9 | 334.6 $\pm$ 119.8        | 326.5 $\pm$ 116.5 | 342.6 $\pm$ 124.0 |
| Baseline NEI VFQ-25 scores (mean $\pm$ SD)           | 71.8 $\pm$ 17.2   | 70.4 $\pm$ 16.6          | 71.1 $\pm$ 17.8   | 69.6 $\pm$ 16.8   | 72.9 $\pm$ 19.1   | 70.3 $\pm$ 19.4          | 74.0 $\pm$ 18.2   | 71.3 $\pm$ 19.1   |

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI VFQ-25 = National Eye Institute 25-Item Visual Functioning Questionnaire; SD = standard deviation.

Table 2. Prespecified Efficacy

|                                                                                                      | VIEW 1             |                          |                        |                       |
|------------------------------------------------------------------------------------------------------|--------------------|--------------------------|------------------------|-----------------------|
|                                                                                                      | Ranibizumab        | Intravitreal Aflibercept |                        |                       |
|                                                                                                      | 0.5q4              | 2q4                      | 0.5q4                  | 2q8                   |
| Primary end point                                                                                    |                    |                          |                        |                       |
| N (PPS)                                                                                              | 269                | 285                      | 270                    | 265                   |
| Proportion maintaining vision (losing <15 ETDRS letters), % (n)                                      | 94.4% (254)        | 95.1% (271)              | 95.9% (259)            | 95.1% (252)           |
| N (full analysis set)                                                                                | 304                | 304                      | 301                    | 301                   |
| Proportion maintaining vision (losing <15 ETDRS letters, LOCF), % (n)                                | 93.8% (285)        | 95.1% (289)              | 95.0% (286)            | 94.4% (284)           |
| Secondary end points                                                                                 |                    |                          |                        |                       |
| N (full analysis set)                                                                                | 304                | 304                      | 301                    | 301                   |
| Change in ETDRS BCVA (mean $\pm$ SD)                                                                 | 8.1 $\pm$ 15.3     | 10.9 $\pm$ 13.8          | 6.9 $\pm$ 13.4         | 7.9 $\pm$ 15.0        |
| LS mean difference between IAI and ranibizumab (95% CI)*                                             |                    | 3.15 (0.92 to 5.37)      | -0.80 (-3.03 to 1.43)  | 0.26 (-1.97 to 2.49)  |
| Proportion gaining $\geq$ 15 ETDRS letters, % (n)                                                    | 30.9% (94)         | 37.5% (114)              | 24.9% (75)             | 30.6% (92)            |
| LS mean difference between IAI and ranibizumab (95% CI)*                                             |                    | 6.58 (-0.98 to 14.14)    | -6.00 (-13.17 to 1.16) | -0.36 (-7.74 to 7.03) |
| Change in CNV area, mm <sup>2</sup> (mean $\pm$ SD)                                                  | -4.2 $\pm$ 5.6     | -4.6 $\pm$ 5.5           | -3.5 $\pm$ 5.3         | -3.4 $\pm$ 6.0        |
| LS mean difference between IAI and ranibizumab (95% CI)*                                             |                    | -0.33 (-1.04 to 0.38)    | 0.71 (-0.01 to 1.42)   | 0.86 (0.15-1.58)      |
| Change in total NEI VFQ-25 score (mean $\pm$ SD)                                                     | 4.9 $\pm$ 14.0     | 6.7 $\pm$ 13.5           | 4.5 $\pm$ 11.9         | 5.1 $\pm$ 14.7        |
| LS mean difference between IAI and ranibizumab (95% CI)*                                             |                    | 1.28 (-0.73 to 3.28)     | -0.67 (-2.69 to 1.35)  | -0.60 (-2.61 to 1.42) |
| Exploratory end point                                                                                |                    |                          |                        |                       |
| Change in central retinal thickness, $\mu$ m (mean $\pm$ SD)                                         | -116.8 $\pm$ 109.0 | -116.5 $\pm$ 98.4        | -115.6 $\pm$ 104.1     | -128.5 $\pm$ 108.5    |
| Post hoc end point <sup>†</sup>                                                                      |                    |                          |                        |                       |
| Proportion with dry retina (absence of cystic intraretinal edema and subretinal fluid on OCT), % (n) | 63.6% (171)        | 64.8% (184)              | 56.7% (148)            | 63.4% (168)           |

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; BCVA = best-corrected visual acuity; aflibercept injection; LOCF = last observation carried forward; LS = least-squares; NEI VFQ-25 = National Eye Institute 25-Item Visual

\*95.1% CI for VIEW 1.

<sup>†</sup>Observed case.

each aflibercept group within the prespecified 10% margin (Fig 2), and the point estimates of the differences in means favoring the aflibercept groups in all cases. All the aflibercept regimens also met the prespecified 7% noninferiority margin in the prespecified integrated analysis combining the 2 VIEW studies, as well as the prespecified 5% margin for clinical equivalence compared with ranibizumab in the individual VIEW studies. Moreover, the results of multiple imputation analyses were consistent with those using the LOCF.

### Mean Changes in Best-Corrected Visual Acuity and Other Visual Acuity End Points

The mean change in BCVA was a clinically important secondary end point in both studies. On the basis of the hierarchical testing sequence, only the aflibercept 2q4 group was statistically superior to ranibizumab, and only in VIEW 1, with a gain of +10.9 versus +8.1 letters (Table 2). Small numeric differences between treatment groups in one study at any given timepoint were not reproduced in the other study, suggesting that they reflected random variability even in groups of this size (Fig 3A, B); this interpretation was supported by a prespecified integrated analysis that combined the 2 studies (Fig 3C), showing similar visual acuity scores

across the entire 52-week study for all treatment groups. All groups behaved similarly in this integrated analysis (Fig 3C), with rapid increases in mean visual acuity after the first injection followed by incremental gains that were durable and maintained through week 52. Regardless of whether the analysis was by LOCF, by multiple imputations, by assessing completers, or by using actual observed data, intravitreal aflibercept dosed every 2 months achieved a mean visual acuity score within 0.3 letters of monthly ranibizumab in the integrated analysis, with a CI of less than 2 letters (Fig 3C, inset).

In both studies, the secondary end point of proportions of patients gaining  $\geq$ 15 ETDRS letters from baseline to week 52 was similar in all treatment groups (Table 2), as were other exploratory categorical measures of visual outcome (Appendix 5, available at <http://aaojournal.org>). Likewise, vision-related quality of life, assessed by the change of total score of the NEI VFQ-25, improved in all groups in both studies (Table 2).

### Key Anatomic Measures

In both studies, all groups demonstrated a comparable decrease in the secondary end point of change in area of active CNV

## Outcomes at Week 52

|                                                                                                      | VIEW 2             |                          |                       |                        |
|------------------------------------------------------------------------------------------------------|--------------------|--------------------------|-----------------------|------------------------|
|                                                                                                      | Ranibizumab        | Intravitreal Aflibercept |                       |                        |
|                                                                                                      | 0.5q4              | 2q4                      | 0.5q4                 | 2q8                    |
| Primary end point                                                                                    |                    |                          |                       |                        |
| N (PPS)                                                                                              | 269                | 274                      | 268                   | 270                    |
| Proportion maintaining vision (losing <15 ETDRS letters), % (n)                                      | 94.4% (254)        | 95.6% (262)              | 96.3% (258)           | 95.6% (258)            |
| N (full analysis set)                                                                                | 291                | 309                      | 296                   | 306                    |
| Proportion maintaining vision (losing <15 ETDRS letters, LOCF), % (n)                                | 94.8% (276)        | 94.5% (292)              | 95.3% (282)           | 95.4% (292)            |
| Secondary end points                                                                                 |                    |                          |                       |                        |
| N (full analysis set)                                                                                | 291                | 309                      | 296                   | 306                    |
| Change in ETDRS BCVA (mean $\pm$ SD)                                                                 | 9.4 $\pm$ 13.5     | 7.6 $\pm$ 12.6           | 9.7 $\pm$ 14.1        | 8.9 $\pm$ 14.4         |
| LS mean difference between IAI and ranibizumab (95% CI)*                                             |                    | -1.95 (-4.10 to 0.20)    | -0.06 (-2.24 to 2.12) | -0.90 (-3.06 to 1.26)  |
| Proportion gaining $\geq$ 15 ETDRS letters, % (n)                                                    | 34.0% (99)         | 29.4% (91)               | 34.8% (103)           | 31.4% (96)             |
| LS mean difference between IAI and ranibizumab (95% CI)*                                             |                    | -4.57 (-12.02 to 2.88)   | 0.78 (-6.91 to 8.46)  | -2.65 (-10.18 to 4.88) |
| Change in CNV area, mm <sup>2</sup> (mean $\pm$ SD)                                                  | -4.2 $\pm$ 5.9     | -6.0 $\pm$ 6.1           | -4.2 $\pm$ 6.1        | -5.2 $\pm$ 5.9         |
| LS mean difference between IAI and ranibizumab (95% CI)*                                             |                    | -1.18 (-1.98 to -0.38)   | 0.17 (-0.63 to 0.97)  | -0.73 (-1.53 to 0.07)  |
| Change in total NEI VFQ-25 score (mean $\pm$ SD)                                                     | 6.3 $\pm$ 14.8     | 4.5 $\pm$ 15.0           | 5.1 $\pm$ 13.7        | 4.9 $\pm$ 14.7         |
| LS mean difference between IAI and ranibizumab (95% CI)*                                             |                    | -2.79 (-4.90 to -0.68)   | -0.93 (-3.07 to 1.20) | -1.95 (-4.07 to 0.17)  |
| Exploratory end point                                                                                |                    |                          |                       |                        |
| Change in central retinal thickness, $\mu$ m (mean $\pm$ SD)                                         | -138.5 $\pm$ 122.2 | -156.8 $\pm$ 122.8       | -129.8 $\pm$ 114.8    | -149.2 $\pm$ 119.7     |
| Post hoc end point <sup>†</sup>                                                                      |                    |                          |                       |                        |
| Proportion with dry retina (absence of cystic intraretinal edema and subretinal fluid on OCT), % (n) | 60.4% (162)        | 80.3% (220)              | 63.9% (170)           | 71.9% (197)            |

CNV = choroidal neovascularization; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal Functioning Questionnaire; OCT = optical coherence tomography; PPS = per protocol set; SD = standard deviation.

(Table 2). Likewise, all aflibercept groups in both studies had reductions in central retinal thickness similar to those for monthly ranibizumab as assessed by OCT, with a large and rapid reduction evident by week 4 (with retinal thickness approaching normal levels) that was maintained to week 52 (Table 2, Fig 4). Minor fluctuations in central retinal thickness were seen in the 2q8 group after sham injections in the VIEW 2 study; these fluctuations attenuated over time, starting at 17  $\mu$ m and decreasing to 8  $\mu$ m over the year, with no apparent negative impact on visual acuity outcomes.

Because of the inability of other regimens in the CATT<sup>13</sup> to match the retinal thickness and retinal fluid improvements seen with monthly ranibizumab, a post hoc analysis was performed to determine the percentage of patients who had fluid-free retinas, which were defined, on OCT, by the absence of both cystic intraretinal edema and subretinal fluid. All intravitreal aflibercept groups were similar to the monthly ranibizumab group in terms of this end point, with numerically higher percentages of dry retinas seen in the 2q4 and 2q8 regimens largely driven by VIEW 2 (Table 2; Appendix 6, available at <http://aaojournal.org>). Integrated analysis combining both studies for proportions of patients with dry retinas for ranibizumab and the aflibercept regimens of 2q4, 0.5q4, and 2q8 showed percentages of 62.0%, 72.4%, 60.3%, and 67.7%, respectively.

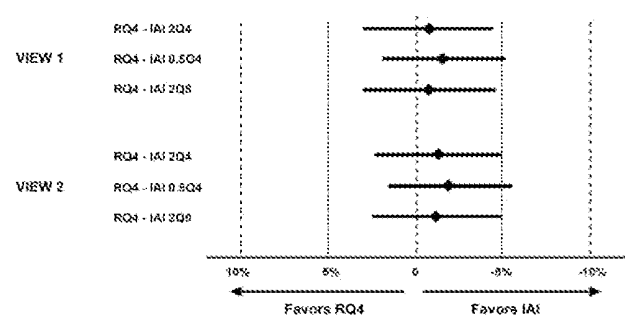


Figure 2. Difference in proportions of patients who maintained vision (losing <15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) at week 52 in the VIEW studies (per protocol set [PPS]). The diamond symbol denotes the difference between the treatment arms, and the horizontal bars indicate 95% confidence interval (CI) range. The CI within the left 10% (dashed vertical lines) indicates that all intravitreal aflibercept arms were noninferior to ranibizumab. The CI within the left 5% (dotted vertical line) indicates clinical equivalence to ranibizumab. The last observation carried forward (LOCF) was used for imputing the missing values. RQ4 = 0.5 mg ranibizumab monthly; 0.5Q4 = 0.5 mg IAI monthly; 2Q4 = 2 mg IAI monthly; 2Q8 = 2 mg IAI every 2 months after 3 initial monthly doses; IAI = intravitreal aflibercept injection.

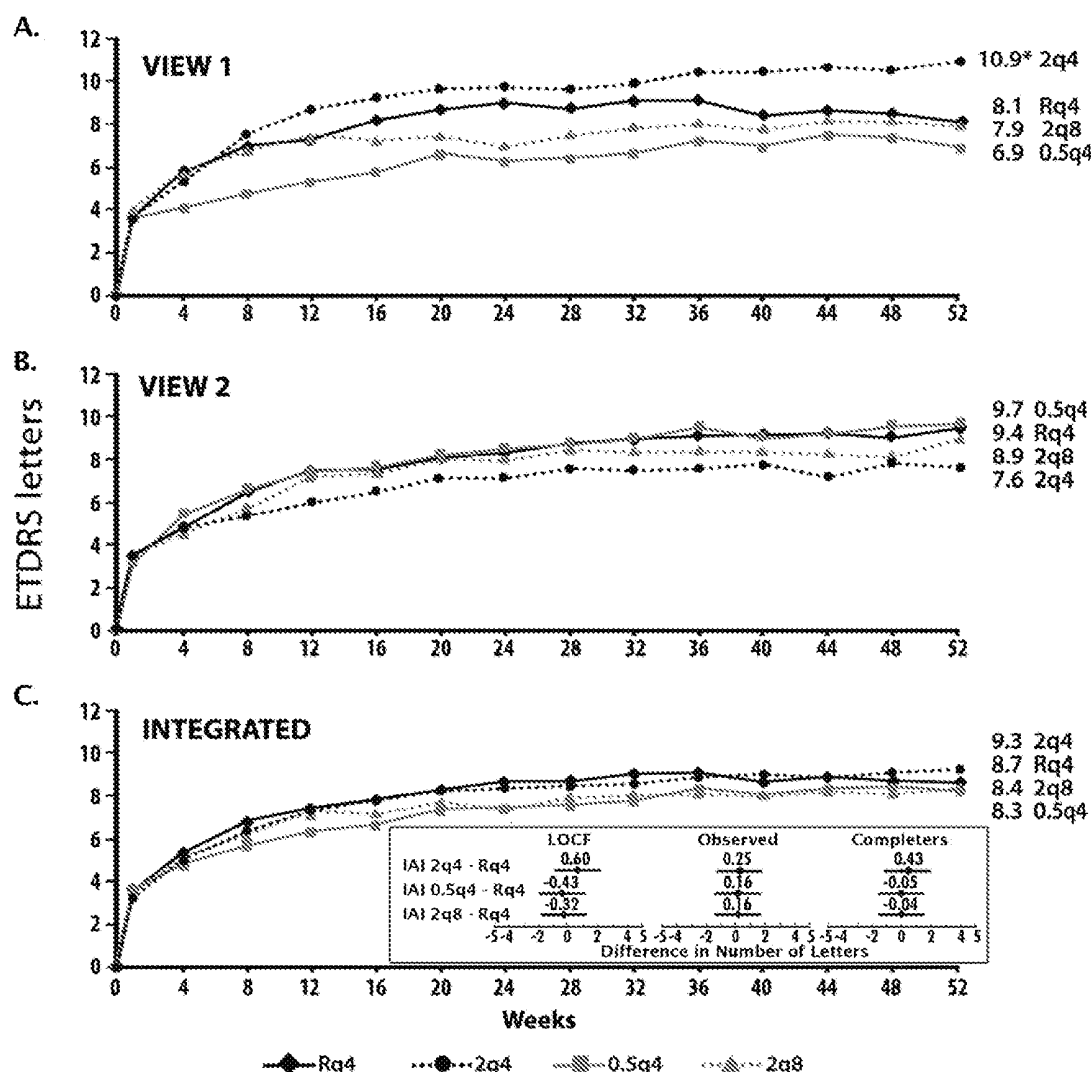


**Figure 3.** Mean change in best-corrected visual acuity (BCVA) from baseline to week 52 in the individual VIEW studies and in the integrated analysis. Values in the line graphs refer to mean changes in the number of letters from baseline at week 52. Only the intravitreal aflibercept 2q4 arm in VIEW 1 was significantly different from ranibizumab (\* $P = 0.005$  for the difference). The panel inset (integrated analysis) shows the difference in visual acuity between each intravitreal aflibercept arm and ranibizumab (least-square mean with 95% confidence interval [CI]) at week 52, using 3 different analyses: by last observation carried forward (LOCF), using observed case data, and by assessing completers. Rq4 = 0.5 mg ranibizumab monthly; 0.5q4 = 0.5 mg IAI monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection.

## Safety

Intravitreal aflibercept was generally well tolerated and had a profile of ocular treatment-emergent adverse experiences, including serious ocular adverse events, similar to those for monthly ranibizumab (Table 3; Appendix 7, available at <http://aaojournal.org>). Differences were noted in the prespecified analyses of intraocular pressure: Fewer patients treated with aflibercept had increases in intraocular pressure over the 52 weeks of the VIEW 1 and VIEW 2 studies (Appendix 7, available at <http://aaojournal.org>). There were few ocular injection-related treatment-emergent serious adverse events in the study eye. The combined data for both studies showed a rate of events/1000 injections of 1.1, 0.8, 0.1, and 0.2 for the ranibizumab 0.5q4 and intravitreal aflibercept 2q4,

0.5q4, and 2q8 groups, respectively. These events included eye disorders, endophthalmitis, procedural complications, and increased intraocular pressure.

There was a similar overall incidence of systemic (nonocular) adverse events (Appendix 7, available at <http://aaojournal.org>), serious systemic adverse events, specific arterial thromboembolic end points as set forth by the Anti-Platelet Trialists' Collaboration, and deaths between intravitreal aflibercept and ranibizumab (Table 3). Among the aflibercept treatment groups, there was no evidence of a dose-response for adverse events: The group with the highest exposure, the aflibercept 2q4 group, generally had the lowest rates of adverse events. There was little to no immunogenicity associated with intravitreal aflibercept (Appendix 8, available at <http://aaojournal.org>).

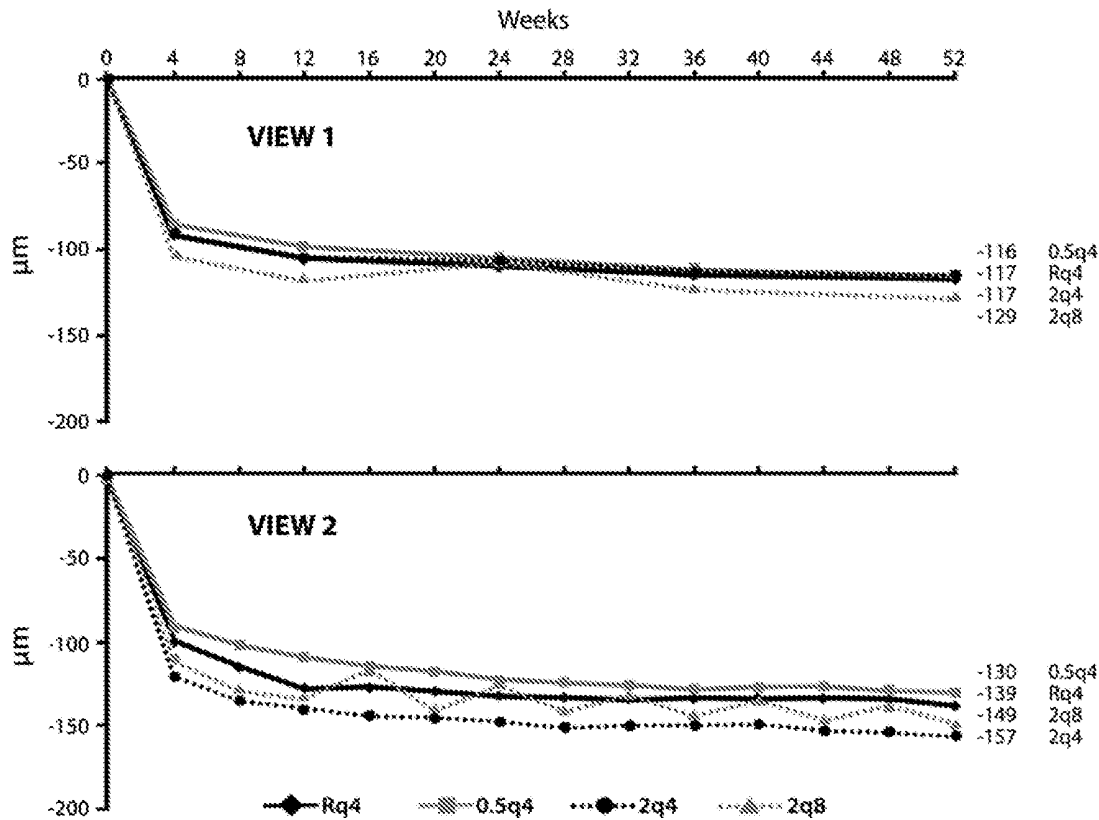


**Figure 4.** Mean change from baseline in central retinal thickness (full analysis set). As described in the “Materials and Methods” section, in VIEW 1, optical coherence tomography (OCT) was performed at screening, at the treatment initiation visit, and at weeks 4, 12, 24, 36, and 52 (and was optional at the investigators’ discretion at other study visits). In VIEW 2, OCT was performed at every study visit. The last observation carried forward (LOCF) was used for imputing the missing values. Rq4 = 0.5 mg ranibizumab monthly; 0.5q4 = 0.5 mg intravitreal aflibercept injection (IAI) monthly; 2q4 = 2 mg IAI monthly; 2q8 = 2 mg IAI every 2 months after 3 initial monthly doses.

## Discussion

We have described 2 large and similarly designed clinical trials involving more than 2400 patients with neovascular AMD. In both trials, all 3 aflibercept treatment regimens (including the every-2-month regimen after 3 initial monthly loading doses) were statistically noninferior to monthly ranibizumab in preventing moderate visual acuity loss at 1 year, meeting the primary outcome of the trials; all the aflibercept regimens also met the stricter margin of 5% for clinical equivalence compared with monthly ranibizumab. In terms of mean change in BCVA over time, all aflibercept regimens behaved similarly to monthly ranibizumab, with rapid increases after the first treatment followed by incremental gains that were durable and maintained through week 52. Mean visual acuity scores were within 1 letter of each other at week 52 in the prespecified integrated analysis combining the 2 studies; of note, aflibercept dosed every 2 months achieved a visual acuity score within 0.3 letters of monthly ranibizumab, with a CI of less than 2 letters, regardless of the analysis set used. Because the CATT<sup>13</sup> highlighted the inability of other regimens, including monthly be-

vacizumab and PRN ranibizumab or bevacizumab, to match the retinal thickness and retinal fluid improvements seen with monthly ranibizumab, it is notable that all 3 aflibercept regimens behaved similarly to monthly ranibizumab in terms of these anatomic measures.

Because of the large treatment burden, extensive efforts have been devoted toward developing an optimized treatment paradigm that avoids the need for monthly injections or monitoring visits. The CATT and HARBOR studies used noninferiority margins of change from baseline BCVA of 5 letters and 4 letters, respectively, to evaluate the efficacy of PRN regimens (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677).<sup>13</sup> The CATT<sup>13</sup> generated much interest, in part because it showed that PRN ranibizumab and bevacizumab regimens approached the visual acuity outcomes achieved with monthly ranibizumab; however, these PRN regimens produced numerically smaller gains in BCVA at 52 weeks (by 1.7–2.6 letters) with poorer anatomic outcomes. Switching from a monthly to a PRN regimen during the second year of the CATT significantly worsened visual and anatomic out-

Table 3. Serious Ocular Adverse Events in the Study Eye and Other Key Nonocular Events Occurring in  $\geq 0.5\%$ \* of Patients in Any Study Arm

|                                               | VIEW 1      |           |                          |           | VIEW 2      |           |                          |           |
|-----------------------------------------------|-------------|-----------|--------------------------|-----------|-------------|-----------|--------------------------|-----------|
|                                               | Ranibizumab |           | Intravitreal Aflibercept |           | Ranibizumab |           | Intravitreal Aflibercept |           |
|                                               | 0.5q4       | 2q4       | 0.5q4                    | 2q8       | 0.5q4       | 2q4       | 0.5q4                    | 2q8       |
| N (safety analysis set)                       | 304         | 304       | 304                      | 303       | 291         | 309       | 297                      | 307       |
| Patients with at least 1 ocular SAE, n (%)    | 10 (3.3)    | 7 (2.3)   | 6 (2.0)                  | 3 (1.0)   | 9 (3.1)     | 6 (1.9)   | 5 (1.7)                  | 9 (2.9)   |
| Serious ocular adverse event, n (%)           |             |           |                          |           |             |           |                          |           |
| Endophthalmitis                               | 3 (1.0)     | 3 (1.0)   | 0                        | 0         | 0           | 0         | 0                        | 0         |
| Visual acuity reduced                         | 2 (0.7)     | 1 (0.3)   | 2 (0.7)                  | 0         | 1 (0.3)     | 1 (0.3)   | 1 (0.3)                  | 5 (1.6)   |
| Retinal hemorrhage                            | 2 (0.7)     | 0         | 0                        | 2 (0.7)   | 1 (0.3)     | 2 (0.6)   | 1 (0.3)                  | 1 (0.3)   |
| Posterior capsule opacification               | —           | —         | —                        | —         | 2 (0.7)     | 0         | 0                        | 0         |
| Serious systemic (or nonocular) adverse event | 57 (18.8)   | 40 (13.2) | 50 (16.4)                | 51 (16.8) | 26 (8.9)    | 36 (11.7) | 37 (12.5)                | 38 (12.4) |
| APTC ATE events                               |             |           |                          |           |             |           |                          |           |
| Any APTC ATE event                            | 5 (1.6)     | 2 (0.7)   | 7 (2.3)                  | 6 (2.0)   | 5 (1.7)     | 4 (1.3)   | 5 (1.7)                  | 8 (2.6)   |
| Vascular death                                | 1 (0.3)     | 0         | 1 (0.3)                  | 4 (1.3)   | 1 (0.3)     | 1 (0.3)   | 2 (0.7)                  | 1 (0.3)   |
| Nonfatal myocardial infarction                | 4 (1.3)     | 1 (0.3)   | 4 (1.3)                  | 1 (0.3)   | 2 (0.7)     | 2 (0.6)   | 2 (0.7)                  | 5 (1.6)   |
| Nonfatal stroke                               | 0           | 1 (0.3)   | 2 (0.7)                  | 1 (0.3)   | 2 (0.7)     | 1 (0.3)   | 1 (0.3)                  | 2 (0.7)   |
| Any AE of hypertension                        | 29 (9.5)    | 25 (8.2)  | 26 (8.6)                 | 31 (10.2) | 29 (10.0)   | 31 (10.0) | 22 (7.4)                 | 28 (9.1)  |
| SAEs of interest occurring in any patient     |             |           |                          |           |             |           |                          |           |
| Venous thromboembolic event                   | 1 (0.3%)    | 0         | 1 (0.3%)                 | 0         | 0           | 0         | 0                        | 0         |
| Congestive heart failure event                | 2 (0.7%)    | 1 (0.3%)  | 2 (0.7%)                 | 3 (1.0%)  | 1 (0.3%)    | 0         | 0                        | 1 (0.3%)  |
| GI perforation or fistula event               | 0           | 0         | 0                        | 0         | 0           | 0         | 1 (0.3%)                 | 1 (0.3%)  |
| Nonocular hemorrhagic event                   | 1 (0.3%)    | 1 (0.3%)  | 3 (1.0%)                 | 3 (1.0%)  | 0           | 2 (0.6%)  | 0                        | 1 (0.3%)  |
| Delayed wound healing                         | 0           | 0         | 0                        | 0         | 0           | 0         | 0                        | 0         |

0.5q4 = 0.5 mg monthly; 2q4 = 2 mg monthly; 2q8 = 2 mg every 2 months after 3 initial monthly doses; AE = adverse event; APTC ATE = Anti-platelet Trialists' Collaboration Arteriothrombotic Event; GI = gastrointestinal; SAE = serious adverse event.

\*For SAEs of interest, occurrence in any patient is reported.

comes and resulted in a decrease in the proportion of patients without retinal fluid.<sup>14</sup> The results from the HARBOR study showed that PRN regimens of ranibizumab (including a higher 2 mg dose) did not achieve noninferiority compared with monthly ranibizumab (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 3677). Moreover, the PRN regimens in both CATT and HARBOR still required mandatory monthly visits, during which treatment decisions had to be made largely on the basis of anatomic measures. The demonstration that monthly aflibercept provides similar efficacy and safety as the current approved standard of monthly ranibizumab is important, but the finding that remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians. The FDA has approved intravitreal aflibercept injection for AMD and recommended the regimen of 2 mg once every 2 months after 3 initial monthly doses (Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2011. Available at: <http://www.regeneron.com/Eylea/eylea-fpi.pdf>. Accessed August 8, 2012). This approval was based on the evaluation that this regimen provided the best benefit/risk; the approved label notes that aflibercept can be dosed as often as every 4 weeks, although additional efficacy was not reported with such frequent dosing. By halving the need for monthly visits, the every-2-month regimen of aflibercept may markedly decrease the treatment burden experienced by patients and their families. Less frequent

injections also should provide an ocular safety benefit. Although the VIEW studies were not powered to see differences in rare but serious intraocular complications (e.g., endophthalmitis and retinal detachment), it is likely that fewer injections may substantially decrease the cumulative population risk of such events, considering that millions of injections are given each year.

After the 1-year primary end point of VIEW 1/VIEW 2 presented in this article, all treatment groups' dosing intervals were changed to a common protocol of modified quarterly dosing with their originally randomized dose and drug (all patients were monitored monthly and received a minimum of dosing every 12 weeks with interim as-needed monthly intravitreal injections). The results of this second year were recently presented (Invest Ophthalmol Vis Sci 2012;53:E-Abstract 6962) and reveal 81.6% to 85.7% patient retention in all groups with comparable visual acuity maintenance (91%–92%) in each group at the 96-week time point. The total number of active injections (baseline to week 96) was 16.0 to 16.2 in the monthly intravitreal aflibercept groups, 16.5 in the monthly ranibizumab group, and 11.2 in the original 2q8 group. The finding that visual acuity maintenance can be achieved for up to 96 weeks in the 2q8 group with similar gains in BCVA compared with ranibizumab despite more than 5 fewer doses is encouraging and implies that the treatment burden of neovascular AMD may be meaningfully reduced with this 2q8 intravitreal aflibercept regimen.

The sustained durability of intravitreal aflibercept as demonstrated by the every-2-month regimen is consistent

with the rationale that a higher binding affinity could lead to increased durability.<sup>17</sup> It is encouraging that the increased affinity of intravitreal aflibercept did not result in an observed increase in ocular or systemic adverse events. In the VIEW 1 and VIEW 2 trials, no differences in systemic or ocular safety were noted between any of the doses or dosing regimens of intravitreal aflibercept. Systemic exposure of aflibercept injected intravitreally is extremely low (Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2011. Available at: <http://www.regeneron.com/Eylea/eylea-fpi.pdf>. Accessed August 8, 2012). After intravitreal administration of 2 mg per eye of aflibercept to patients with wet AMD, the mean maximum concentration of free aflibercept in the plasma was 0.02 µg/ml (range, 0–0.054 µg/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 repeated doses 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.

In conclusion, intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as similar safety and tolerability. Intravitreal aflibercept dosed every 2 months has the potential to provide patients, their families, and clinicians the opportunity for the optimal vision gains and anatomic disease control they have come to expect from monthly ranibizumab, with a substantially decreased treatment and compliance burden, and a lower cumulative risk of injection-related adverse events.

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## Footnotes and Financial Disclosures

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The author(s) have made the following disclosure(s): J.S.H. is a consultant to and has received research funding from Alimera, Allergan, Fovea, Genentech, Genzyme, GlaxoSmithKline, Neovista, and Regeneron Pharmaceuticals. He has also received travel support from Regeneron Pharmaceuticals. D.M.B. is a consultant to Alimera, Allergan, Bayer, Genentech/Roche, Novartis, Regeneron Pharmaceuticals, and Thrombogenics and has received research funding from Alcon, Alimera, Allergan, Eli Lilly, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, and Thrombogenics. He has also received travel support from Regeneron Pharmaceuticals and lecture fees from Genentech. V.C. is a consultant to Alimera and Bayer and has received research funding from Alcon, Allergan, Bayer, Novartis, and Pfizer. He is an advisory board member for Allergan and Novartis and has also received travel support from Bayer. J.-F.K. is a consultant to Alcon, Bayer, and Thea and an advisory board member for Allergan, Bayer, and Novartis. He has received travel support from Regeneron Pharmaceuticals. P.K.K. is a consultant to Bayer, Genentech, Novartis, and Regeneron Pharmaceuticals. He has received research funding from Regeneron Pharmaceuticals. Q.D.N. is a consultant to Bausch & Lomb and Santen and has received research funding from

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G.D.Y. and N.S., incorporating the advice of a panel of academic and physician experts, developed the initial proposal for the VIEW 1 study design. The study design of both studies was further developed and finalized by the academic authors and clinical and statistical authors from Regeneron Pharmaceuticals and Bayer HealthCare (sponsors). The sponsors conducted the trials and together with the investigators gathered the data. Study conduct and analyses were supervised by the Study Steering Committees and the sponsors. The Writing Committee consisting of authors J.S.H., D.M.B., V.C., and U.S.-E. (subteam of VIEW Steering Committees) along with G.D.Y. composed the first draft of the paper, which was critically revised and finalized by the input of all coauthors. The Writing Committee members and all other authors met authorship criteria. All coauthors had full and unrestricted access to the data and decided to publish the paper vouching for the accuracy and completeness of the reported data.

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**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING  
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Docket Number (Optional)

**REGN-008CIPCON2**

In re Application of: **YANCOPOULOS, GEORGE D.**

Application No.: **15/471,506**

Filed: **March 28, 2017**

For: **Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders**

The owner\*, **REGENERON PHARMACEUTICALS, INC.**, of **100** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. **9,669,069 and 9,254,338**, as the term of said **prior patent** is presently shortened

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Signature

**June 25, 2018**

Date

Karl Bozicevic

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**650-833-7735**

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|---------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|--------------------------------------------|------------------------------------|---------------------------|---------------|---------------------------------------|-----------|-----------------|---------------------|---|--|
| <b>PATENT APPLICATION FEE DETERMINATION RECORD</b><br>Substitute for Form PTO-875                                               |                                                                                          |                                                                                                                                                                                                                               |                                  | Application or Docket Number<br>15/471,506 |                                    | Filing Date<br>03/28/2017 |               | <input type="checkbox"/> To be Mailed |           |                 |                     |   |  |
| ENTITY: <input checked="" type="checkbox"/> LARGE <input type="checkbox"/> SMALL <input type="checkbox"/> MICRO                 |                                                                                          |                                                                                                                                                                                                                               |                                  |                                            |                                    |                           |               |                                       |           |                 |                     |   |  |
| <b>APPLICATION AS FILED - PART I</b>                                                                                            |                                                                                          |                                                                                                                                                                                                                               |                                  |                                            |                                    |                           |               |                                       |           |                 |                     |   |  |
|                                                                                                                                 |                                                                                          | (Column 1)                                                                                                                                                                                                                    |                                  | (Column 2)                                 |                                    |                           |               |                                       |           |                 |                     |   |  |
| FOR                                                                                                                             |                                                                                          | NUMBER FILED                                                                                                                                                                                                                  |                                  | NUMBER EXTRA                               |                                    | RATE (\$)                 |               | FEE (\$)                              |           |                 |                     |   |  |
| <input type="checkbox"/> BASIC FEE<br>(37 CFR 1.16(a), (b), or (c))                                                             |                                                                                          | N/A                                                                                                                                                                                                                           |                                  | N/A                                        |                                    | N/A                       |               |                                       |           |                 |                     |   |  |
| <input type="checkbox"/> SEARCH FEE<br>(37 CFR 1.16(k), (l), or (m))                                                            |                                                                                          | N/A                                                                                                                                                                                                                           |                                  | N/A                                        |                                    | N/A                       |               |                                       |           |                 |                     |   |  |
| <input type="checkbox"/> EXAMINATION FEE<br>(37 CFR 1.16(o), (p), or (q))                                                       |                                                                                          | N/A                                                                                                                                                                                                                           |                                  | N/A                                        |                                    | N/A                       |               |                                       |           |                 |                     |   |  |
| TOTAL CLAIMS<br>(37 CFR 1.16(i))                                                                                                |                                                                                          | minus 20 = *                                                                                                                                                                                                                  |                                  |                                            |                                    | x \$80 =                  |               |                                       |           |                 |                     |   |  |
| INDEPENDENT CLAIMS<br>(37 CFR 1.16(h))                                                                                          |                                                                                          | minus 3 = *                                                                                                                                                                                                                   |                                  |                                            |                                    | x \$420 =                 |               |                                       |           |                 |                     |   |  |
| <input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))                                                                  |                                                                                          | If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). |                                  |                                            |                                    |                           |               |                                       |           |                 |                     |   |  |
| <input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))                                                      |                                                                                          |                                                                                                                                                                                                                               |                                  |                                            |                                    |                           |               |                                       |           |                 |                     |   |  |
| * If the difference in column 1 is less than zero, enter "0" in column 2.                                                       |                                                                                          |                                                                                                                                                                                                                               |                                  |                                            |                                    | TOTAL                     |               |                                       |           |                 |                     |   |  |
| <b>APPLICATION AS AMENDED - PART II</b>                                                                                         |                                                                                          |                                                                                                                                                                                                                               |                                  |                                            |                                    |                           |               |                                       |           |                 |                     |   |  |
|                                                                                                                                 |                                                                                          | (Column 1)                                                                                                                                                                                                                    |                                  | (Column 2)                                 |                                    | (Column 3)                |               |                                       |           |                 |                     |   |  |
| <b>AMENDMENT</b>                                                                                                                | 06/25/2018                                                                               |                                                                                                                                                                                                                               | CLAIMS REMAINING AFTER AMENDMENT |                                            | HIGHEST NUMBER PREVIOUSLY PAID FOR |                           | PRESENT EXTRA |                                       | RATE (\$) |                 | ADDITIONAL FEE (\$) |   |  |
|                                                                                                                                 | Total<br>(37 CFR 1.16(i))                                                                |                                                                                                                                                                                                                               | * 26                             |                                            | Minus ** 26                        |                           | = 0           |                                       | x \$100 = |                 | 0                   |   |  |
|                                                                                                                                 | Independent<br>(37 CFR 1.16(h))                                                          |                                                                                                                                                                                                                               | * 2                              |                                            | Minus *** 3                        |                           | = 0           |                                       | x \$460 = |                 | 0                   |   |  |
|                                                                                                                                 | <input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))                           |                                                                                                                                                                                                                               |                                  |                                            |                                    |                           |               |                                       |           |                 |                     |   |  |
|                                                                                                                                 | <input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) |                                                                                                                                                                                                                               |                                  |                                            |                                    |                           |               |                                       |           |                 |                     |   |  |
|                                                                                                                                 |                                                                                          |                                                                                                                                                                                                                               |                                  |                                            |                                    |                           |               |                                       |           | TOTAL ADD'L FEE |                     | 0 |  |
|                                                                                                                                 |                                                                                          | (Column 1)                                                                                                                                                                                                                    |                                  | (Column 2)                                 |                                    | (Column 3)                |               |                                       |           |                 |                     |   |  |
| <b>AMENDMENT</b>                                                                                                                |                                                                                          |                                                                                                                                                                                                                               | CLAIMS REMAINING AFTER AMENDMENT |                                            | HIGHEST NUMBER PREVIOUSLY PAID FOR |                           | PRESENT EXTRA |                                       | RATE (\$) |                 | ADDITIONAL FEE (\$) |   |  |
|                                                                                                                                 | Total<br>(37 CFR 1.16(i))                                                                |                                                                                                                                                                                                                               | *                                |                                            | Minus **                           |                           | =             |                                       | x \$0 =   |                 |                     |   |  |
|                                                                                                                                 | Independent<br>(37 CFR 1.16(h))                                                          |                                                                                                                                                                                                                               | *                                |                                            | Minus ***                          |                           | =             |                                       | x \$0 =   |                 |                     |   |  |
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|----------------------------------------------------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------|--|
| <b>Application Number</b><br> | <b>Application/Control No.</b><br>15/471,506 | <b>Applicant(s)/Patent under Reexamination</b><br>YANCOPOULOS, GEORGE D. |  |
| <b>Document Code - DISQ</b>                                                                                    |                                              | <b>Internal Document – DO NOT MAIL</b>                                   |  |

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REDWOOD CITY, CALIFORNIA 94065  
UNITED STATES OF AMERICA

|                         |              |
|-------------------------|--------------|
| EXAMINER                |              |
| LOCKARD, JON MCCLELLAND |              |
| ART UNIT                | PAPER NUMBER |

1647

DATE MAILED: 07/26/2018

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR  | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|-----------------------|---------------------|------------------|
| 15/471,506      | 03/28/2017  | George D. YANCOPOULOS | REGN-008CIPCON2     | 8014             |

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

| APPLN. TYPE    | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE   |
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| (Date)             |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR  | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|-----------------------|---------------------|------------------|
| 15/471,506      | 03/28/2017  | George D. YANCOPOULOS | REGN-008CIPCON2     | 8014             |

TITLE OF INVENTION: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

| APPLN. TYPE    | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE   |
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| nonprovisional | UNDISCOUNTED  | \$1000        | \$0.00              | \$0.00               | \$1000           | 10/26/2018 |

| EXAMINER                | ART UNIT | CLASS-SUBCLASS |
|-------------------------|----------|----------------|
| LOCKARD, JON MCCLELLAND | 1647     | 424-134100     |

|                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).</p> <p><input type="checkbox"/> Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.</p> <p><input type="checkbox"/> "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. <b>Use of a Customer Number is required.</b></p> | <p>2. For printing on the patent front page, list</p> <p>(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,</p> <p>(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.</p> <p>1 _____</p> <p>2 _____</p> <p>3 _____</p> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## **3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)**

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

## **4a. The following fee(s) are submitted:**

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies \_\_\_\_\_

## **4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)**

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number \_\_\_\_\_ (enclose an extra copy of this form).

## **5. Change in Entity Status (from status indicated above)**

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

**NOTE:** Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

**NOTE:** If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

**NOTE:** Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

**NOTE:** This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature \_\_\_\_\_ Date \_\_\_\_\_

Typed or printed name \_\_\_\_\_ Registration No. \_\_\_\_\_



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|                                                                                                                                                 |             |                       |                         |                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-----------------------|-------------------------|------------------|
| APPLICATION NO.                                                                                                                                 | FILING DATE | FIRST NAMED INVENTOR  | ATTORNEY DOCKET NO.     | CONFIRMATION NO. |
| 15/471,506                                                                                                                                      | 03/28/2017  | George D. YANCOPOULOS | REGN-008CIPCON2         | 8014             |
| 96387                                                                                                                                           | 7590        | 07/26/2018            | EXAMINER                |                  |
| Regeneron - Bozicevic, Field & Francis<br>201 REDWOOD SHORES PARKWAY<br>SUITE 200<br>REDWOOD CITY, CALIFORNIA 94065<br>UNITED STATES OF AMERICA |             |                       | LOCKARD, JON MCCLELLAND |                  |
|                                                                                                                                                 |             |                       | ART UNIT                | PAPER NUMBER     |
|                                                                                                                                                 |             |                       | 1647                    |                  |
| DATE MAILED: 07/26/2018                                                                                                                         |             |                       |                         |                  |

## Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

|                                                                   |                                        |                                       |  |
|-------------------------------------------------------------------|----------------------------------------|---------------------------------------|--|
| <b><i>Notice Requiring Inventor's<br/>Oath or Declaration</i></b> | Application No.<br>15/471,506          | Applicant(s)<br>George D. YANCOPOULOS |  |
|                                                                   | Examiner<br>LOCKARD, JON<br>MCCLELLAND | Art Unit<br>1647                      |  |

This notice is an attachment to the Notice of Allowability (PTOL-37), or the Notice of Allowability For A Design Application (PTOL-37D).

An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor has not yet been submitted.

An oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each inventor (for any inventor for which a compliant oath, declaration, or substitute statement has not yet been submitted) **MUST** be filed no later than the date on which the issue fee is paid. See 35 U.S.C. 115(f). Failure to timely comply will result in ABANDONMENT of this application.

A properly executed inventor's oath to declaration has not been received for the following inventor(s):

If applicant previously filed one or more oaths, declarations, or substitute statements, applicant may have received an informational notice regarding deficiencies therein.

The following deficiencies are noted:

#### INFORMAL ACTION PROBLEMS

- A properly executed inventor's oath or declaration has not been received for the following inventor(s): **George D. YANCOPOULOS**.

Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

### Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

|                               |                                      |                                               |                         |
|-------------------------------|--------------------------------------|-----------------------------------------------|-------------------------|
| <b>Notice of Allowability</b> | <b>Application No.</b><br>15/471,506 | <b>Applicant(s)</b><br>YANCOPOULOS, George D. |                         |
|                               | <b>Examiner</b><br>JON M LOCKARD     | <b>Art Unit</b><br>1647                       | <b>AIA Status</b><br>No |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--**

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the Amendment filed 25 June 2018.  
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_\_.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_\_; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 21-46 (renumbered as claims 1-26, respectively). As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see [http://www.uspto.gov/patents/init\\_events/pph/index.jsp](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a) ☐ All      b) ☐ Some      \*c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_\_.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.  
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.  
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_\_.

**Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

|                                                                                                                   |                                                                           |
|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892)                                                  | 5. <input type="checkbox"/> Examiner's Amendment/Comment                  |
| 2. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),<br>Paper No./Mail Date _____.          | 6. <input type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit<br>of Biological Material _____. | 7. <input type="checkbox"/> Other _____.                                  |
| 4. <input type="checkbox"/> Interview Summary (PTO-413),<br>Paper No./Mail Date. _____.                           |                                                                           |

|                                   |                                                       |
|-----------------------------------|-------------------------------------------------------|
| /J.L./<br>Examiner, Art Unit 1647 | /CHRISTINE J SAUD/<br>Primary Examiner, Art Unit 1647 |
|-----------------------------------|-------------------------------------------------------|

|                                                                                                                  |                                              |                                                                          |
|------------------------------------------------------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------|
| <b>Issue Classification</b><br> | <b>Application/Control No.</b><br>15/471,506 | <b>Applicant(s)/Patent Under Reexamination</b><br>YANCOPOULOS, George D. |
|                                                                                                                  | <b>Examiner</b><br>JON M LOCKARD             | <b>Art Unit</b><br>1647                                                  |

| CPC    |   |      |   |      |      |            |
|--------|---|------|---|------|------|------------|
| Symbol |   |      |   |      | Type | Version    |
| A61K   | / | 38   | / | 179  | F    | 2013-01-01 |
| C07K   | / | 16   | / | 22   | I    | 2013-01-01 |
| C07K   | / | 14   | / | 71   | I    | 2013-01-01 |
| A61K   | / | 9    | / | 0048 | I    | 2013-01-01 |
| A61K   | / | 2039 | / | 505  | A    | 2013-01-01 |
| C07K   | / | 2319 | / | 30   | A    | 2013-01-01 |
| C07K   | / | 2319 | / | 32   | A    | 2013-01-01 |

| CPC Combination Sets |      |     |         |         |
|----------------------|------|-----|---------|---------|
| Symbol               | Type | Set | Ranking | Version |
| /                    | /    |     |         |         |

|                                                                             |                        |                                    |                           |
|-----------------------------------------------------------------------------|------------------------|------------------------------------|---------------------------|
| /JON M LOCKARD/<br>Examiner, Art Unit 1647<br>(Assistant Examiner)          | 19 July 2018<br>(Date) | <b>Total Claims Allowed:</b><br>26 |                           |
| /CHRISTINE J SAUD/<br>Primary Examiner, Art Unit 1647<br>(Primary Examiner) | 22 July 2018<br>(Date) | O.G. Print Claim(s)<br>1           | O.G. Print Figure<br>NONE |

|                                                                                                                  |                                              |                                                                          |  |
|------------------------------------------------------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------|--|
| <b>Issue Classification</b><br> | <b>Application/Control No.</b><br>15/471,506 | <b>Applicant(s)/Patent Under Reexamination</b><br>YANCOPOULOS, George D. |  |
|                                                                                                                  | <b>Examiner</b><br>JON M LOCKARD             | <b>Art Unit</b><br>1647                                                  |  |

|                                     |   |    |       |
|-------------------------------------|---|----|-------|
| <b>INTERNATIONAL CLASSIFICATION</b> |   |    |       |
| <b>CLAIMED</b>                      |   |    |       |
| A61K                                | / | 39 | / 395 |
| A61K                                | / | 38 | / 17  |
| A61K                                | / | 38 | / 18  |
| C07K                                | / | 14 | / 71  |
| <b>NON-CLAIMED</b>                  |   |    |       |
|                                     | / |    | /     |

|                                   |                 |
|-----------------------------------|-----------------|
| <b>US ORIGINAL CLASSIFICATION</b> |                 |
| <b>CLASS</b>                      | <b>SUBCLASS</b> |
|                                   |                 |

|                            |                                          |  |  |  |  |  |
|----------------------------|------------------------------------------|--|--|--|--|--|
| <b>CROSS REFERENCES(S)</b> |                                          |  |  |  |  |  |
| <b>CLASS</b>               | <b>SUBCLASS (ONE SUBCLASS PER BLOCK)</b> |  |  |  |  |  |
|                            |                                          |  |  |  |  |  |

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|-----------------------------------------------------------------------------|------------------------|------------------------------------|---------------------------|
| /JON M LOCKARD/<br>Examiner, Art Unit 1647<br>(Assistant Examiner)          | 19 July 2018<br>(Date) | <b>Total Claims Allowed:</b><br>26 |                           |
| /CHRISTINE J SAUD/<br>Primary Examiner, Art Unit 1647<br>(Primary Examiner) | 22 July 2018<br>(Date) | O.G. Print Claim(s)<br>1           | O.G. Print Figure<br>NONE |

|                                                                                                                         |                                              |                                                                          |
|-------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------|
| <b><i>Issue Classification</i></b><br> | <b>Application/Control No.</b><br>15/471,506 | <b>Applicant(s)/Patent Under Reexamination</b><br>YANCOPOULOS, George D. |
|                                                                                                                         | <b>Examiner</b><br>JON M LOCKARD             | <b>Art Unit</b><br>1647                                                  |

|                                                                                                                                                                                                         |          |       |          |       |          |       |          |       |          |       |          |       |          |       |          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------|----------|-------|----------|-------|----------|-------|----------|-------|----------|-------|----------|-------|----------|
| <input checked="" type="checkbox"/> Claims renumbered in the same order as presented by applicant <input type="checkbox"/> CPA <input checked="" type="checkbox"/> T.D. <input type="checkbox"/> R.1.47 |          |       |          |       |          |       |          |       |          |       |          |       |          |       |          |
| <b>CLAIMS</b>                                                                                                                                                                                           |          |       |          |       |          |       |          |       |          |       |          |       |          |       |          |
| Final                                                                                                                                                                                                   | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
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|                                                                              |                        |                                    |                           |
|------------------------------------------------------------------------------|------------------------|------------------------------------|---------------------------|
| /JON M LOCKARD/<br>Examiner, Art Unit 1647<br>(Assistant Examiner)           | 19 July 2018<br>(Date) | <b>Total Claims Allowed:</b><br>26 |                           |
| /CHRISTINE J SAOUD/<br>Primary Examiner, Art Unit 1647<br>(Primary Examiner) | 22 July 2018<br>(Date) | O.G. Print Claim(s)<br>1           | O.G. Print Figure<br>NONE |

|                                                                                                          |                                              |                                                                          |
|----------------------------------------------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------|
| <b>Search Notes</b><br> | <b>Application/Control No.</b><br>15/471,506 | <b>Applicant(s)/Patent Under Reexamination</b><br>YANCOPOULOS, George D. |
|                                                                                                          | <b>Examiner</b><br>JON M LOCKARD             | <b>Art Unit</b><br>1647                                                  |

| CPC - Searched* |      |          |
|-----------------|------|----------|
| Symbol          | Date | Examiner |
|                 |      |          |

| CPC Combination Sets - Searched* |      |          |
|----------------------------------|------|----------|
| Symbol                           | Date | Examiner |
|                                  |      |          |

| US Classification - Searched* |          |           |          |
|-------------------------------|----------|-----------|----------|
| Class                         | Subclass | Date      | Examiner |
| NONE                          |          | 3/29/2018 | JML      |

\* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes                                                           |           |          |
|------------------------------------------------------------------------|-----------|----------|
| Search Notes                                                           | Date      | Examiner |
| STIC Search of SEQ ID NO:2. See search results in SCORE.               | 3/29/2018 | JML      |
| EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.     | 3/29/2018 | JML      |
| STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history. | 3/29/2018 | JML      |
| PALM: Inventor search.                                                 | 3/29/2018 | JML      |

| Interference Search |                                                          |            |          |
|---------------------|----------------------------------------------------------|------------|----------|
| US Class/CPC Symbol | US Subclass/CPC Group                                    | Date       | Examiner |
|                     | STIC Search of SEQ ID NO:2. See search results in SCORE. | 07/19/2018 | JML      |
|                     | EAST (USPAT): See attached search history.               | 07/19/2018 | JML      |
|                     | PALM: Inventor search.                                   | 07/19/2018 | JML      |

|                                  |  |
|----------------------------------|--|
| /J.L/<br>Examiner, Art Unit 1647 |  |
|----------------------------------|--|

**Inventor Information for 15/471506**

/J.L./

|                        |                  |                      |
|------------------------|------------------|----------------------|
| <b>Inventor Name</b>   | <b>City</b>      | <b>State/Country</b> |
| YANCOPOULOS, GEORGE D. | YORKTOWN HEIGHTS | NEW YORK             |

|            |          |               |                |                 |              |                  |            |         |      |           |        |
|------------|----------|---------------|----------------|-----------------|--------------|------------------|------------|---------|------|-----------|--------|
| Appln Info | Comments | Petition Info | Att/Agent Info | Continuity Data | Foreign Data | <b>Inventors</b> | Applicants | Address | Fees | Post Info | Pre Gr |
|------------|----------|---------------|----------------|-----------------|--------------|------------------|------------|---------|------|-----------|--------|

Search Another: Application #   or Patent #   or International Registration #

PCT /  /   or PG PUBS #

Attorney Docket #

Bar Code #

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**EAST Search History****EAST Search History (I nterference)**

/J.L./

| Ref # | Hits | Search Query                                                                                                        | DBs   | Default Operator | Plurals | Time Stamp       |
|-------|------|---------------------------------------------------------------------------------------------------------------------|-------|------------------|---------|------------------|
| L1    | 2149 | (flt1 or vegfr1 or (vegf adj r1)) same ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3))) | USPAT | OR               | ON      | 2018/07/19 16:45 |
| L2    | 547  | l1 and ((chimer\$ or fusion) same vegf)                                                                             | USPAT | OR               | ON      | 2018/07/19 16:45 |
| L3    | 185  | l1 same ((chimer\$ or fusion) same vegf)                                                                            | USPAT | OR               | ON      | 2018/07/19 16:46 |
| L4    | 2108 | (flt1 or vegfr1 or (vegf adj r1)) with ((flk1 or kdr or vegfr2 or (vegf adj r2)) or (Flt4 vegfr3 or (vegf adj r3))) | USPAT | OR               | ON      | 2018/07/19 16:46 |
| L5    | 98   | l4 with ((chimer\$ or fusion) with vegf)                                                                            | USPAT | OR               | ON      | 2018/07/19 16:46 |
| L6    | 691  | (l4 or l5) and ((eye or ocular or retina\$ or macular) with disorder)                                               | USPAT | OR               | ON      | 2018/07/19 16:46 |
| L7    | 84   | (l3 or l5) and ((eye or ocular or retina\$ or macular) with disorder)                                               | USPAT | OR               | ON      | 2018/07/19 16:46 |
| L8    | 6    | (l3 or l5) same ((eye or ocular or retina\$ or macular) with disorder)                                              | USPAT | OR               | ON      | 2018/07/19 16:47 |
| L9    | 2    | l7 and "l9"                                                                                                         | USPAT | OR               | ON      | 2018/07/19 16:47 |
| L10   | 133  | yancopoulos-g\$.in.                                                                                                 | USPAT | OR               | ON      | 2018/07/19 16:47 |
| L11   | 20   | l7 and l10                                                                                                          | USPAT | OR               | ON      | 2018/07/19 16:47 |
| L12   | 5    | l11 and (eye ocular macular).clm.                                                                                   | USPAT | OR               | ON      | 2018/07/19 16:47 |

**7/ 19/ 2018 4:48:12 PM****C:\Users\jlockard\Documents\EAST\Workspaces\15471506.wsp**



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|                                                                                                                                |             |                       |                                     |                  |
|--------------------------------------------------------------------------------------------------------------------------------|-------------|-----------------------|-------------------------------------|------------------|
| APPLICATION NO.                                                                                                                | FILING DATE | FIRST NAMED INVENTOR  | ATTORNEY DOCKET NO.                 | CONFIRMATION NO. |
| 15/471,506                                                                                                                     | 03/28/2017  | George D. YANCOPOULOS | REGN-008CIPCON2                     | 8014             |
| 7590 08/03/2018<br>Regeneron - Bozicevic, Field & Francis<br>201 REDWOOD SHORES PARKWAY<br>SUITE 200<br>REDWOOD CITY, CA 94065 |             |                       | EXAMINER<br>LOCKARD, JON MCCLELLAND |                  |
|                                                                                                                                |             |                       | ART UNIT                            | PAPER NUMBER     |
|                                                                                                                                |             |                       | 1647                                |                  |
|                                                                                                                                |             |                       | NOTIFICATION DATE                   | DELIVERY MODE    |
|                                                                                                                                |             |                       | 08/03/2018                          | ELECTRONIC       |

## Letter Withdrawing a Notice Requiring Inventor's Oath or Declaration

The Notice Requiring Inventor's Oath or Declaration mailed on 7/26/18 was sent in error, and is hereby withdrawn. The time period set forth in the Notice of Allowance and Fee(s) Due to file a reply and pay the required fees continues to run from the mailing date of the Notice of Allowance and Fee(s) Due. Any time period set forth in the Notice of Allowability continues to run from the mailing date of the Notice of Allowability.

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

(571)-272-4200 or 1(888)-786-0101

Patent Publication Branch

Office of Data Management

Document Description: Issue Fee Payment (PTO-85B)

**Issue Fee Transmittal Form**

| Application Number | Filing Date | First Named Inventor | Atty. Docket No. | Confirmation No. |
|--------------------|-------------|----------------------|------------------|------------------|
| 15471506           | 28-Mar-2017 | George YANCOPOULOS   | REGN-008CIPCON2  | 8014             |

**TITLE OF INVENTION :**

USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

| Entity Status        | Application Type            | Art Unit         | Class - Subclass | EXAMINER       |
|----------------------|-----------------------------|------------------|------------------|----------------|
| Regular Undiscounted | Utility under 35 USC 111(a) | 1647             | 134100           | JON LOCKARD    |
| Issue Fee Due        | Publication Due             | Total Fee(s) Due | Date Due         | Prev. Paid Fee |
| \$1000               | \$0                         | \$1000           | 26-Oct-2018      | \$0            |

**1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)**

| Current Correspondence Address:                                                                                                                                                          | Current Indicated Fee Address :                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| 96387<br>Regeneron - Bozicevic, Field & Francis<br><br>201 REDWOOD SHORES PARKWAY<br>SUITE 200<br>REDWOOD CITY CA 94065<br>UNITED STATES<br>650 327 3400<br><del>doctet@bozpat.com</del> |                                                                                                     |
| <input type="checkbox"/> Change of correspondence address requested, system generated AIA/122-EFS form attached                                                                          | <input type="checkbox"/> Fee Address indication requested, system generated SB/47-EFS form attached |

**2.Entity Status****Change in Entity Status**

- ☐ Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.  
 Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27.  
 Note: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☒ Applicant changing to regular undiscounted fee status.  
 Note: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

WEB IFEE 1.0

Document Description: Issue Fee Payment (PTO-85B)

**3.The Following Fee(s) Are Submitted:**☒ Issue Fee☐ I authorize USPTO to apply my previously paid issue fee to the current fees due☐ Publication Fee☐ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number \_\_\_\_\_☐ Advance Order - # of copies \_\_\_\_\_

If **in addition to** the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency or credit any overpayment, to Deposit Account Number 50-0815.

☒ The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

**4.Firm and/or Attorney Names To Be Printed****NOTE: If no name is listed, no name will be printed**

For printing on the patent front page, list to be displayed as entered

1. Karl Bozicevic

2. Bozicevic, Field &amp; Francis LLP

3.

**5.Assignee Name(s) and Residence Data To Be Printed**

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

| Name                            | City      | State    | Country       | Category    |
|---------------------------------|-----------|----------|---------------|-------------|
| REGENERON PHARMACEUTICALS, INC. | Tarrytown | NEW YORK | united states | corporation |

**6.Signature**

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

|           |                          |                     |            |
|-----------|--------------------------|---------------------|------------|
| Signature | /Karl Bozicevic, 28,807/ | Date                | 10-17-2018 |
| Name      | Karl Bozicevic           | Registration Number | 28807      |

| Electronic Patent Application Fee Transmittal      |                 |                                                            |               |                             |
|----------------------------------------------------|-----------------|------------------------------------------------------------|---------------|-----------------------------|
| <b>Application Number:</b>                         |                 | 15471506                                                   |               |                             |
| <b>Filing Date:</b>                                |                 | 28-Mar-2017                                                |               |                             |
| <b>Title of Invention:</b>                         |                 | USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS |               |                             |
| <b>First Named Inventor/Applicant Name:</b>        |                 | George D. YANCOPOULOS                                      |               |                             |
| <b>Filer:</b>                                      |                 | Karl Bozicevic/Savanna Fuentes                             |               |                             |
| <b>Attorney Docket Number:</b>                     |                 | REGN-008CIPCON2                                            |               |                             |
| Filed as Large Entity                              |                 |                                                            |               |                             |
| <b>Filing Fees for Utility under 35 USC 111(a)</b> |                 |                                                            |               |                             |
| <b>Description</b>                                 | <b>Fee Code</b> | <b>Quantity</b>                                            | <b>Amount</b> | <b>Sub-Total in USD(\$)</b> |
| <b>Basic Filing:</b>                               |                 |                                                            |               |                             |
| UTILITY APPL ISSUE FEE                             | 1501            | 1                                                          | 1000          | 1000                        |
| PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL             | 1504            | 1                                                          | 0             | 0                           |
| <b>Pages:</b>                                      |                 |                                                            |               |                             |
| <b>Claims:</b>                                     |                 |                                                            |               |                             |
| <b>Miscellaneous-Filing:</b>                       |                 |                                                            |               |                             |
| <b>Petition:</b>                                   |                 |                                                            |               |                             |
| <b>Patent-Appeals-and-Interference:</b>            |                 |                                                            |               |                             |

| Description                       | Fee Code | Quantity | Amount | Sub-Total in USD(\$) |
|-----------------------------------|----------|----------|--------|----------------------|
| Post-Allowance-and-Post-Issuance: |          |          |        |                      |
| Extension-of-Time:                |          |          |        |                      |
| Miscellaneous:                    |          |          |        |                      |
| Total in USD (\$)                 |          |          |        | 1000                 |

## Electronic Acknowledgement Receipt

|                                             |                                                            |
|---------------------------------------------|------------------------------------------------------------|
| <b>EFS ID:</b>                              | 34033707                                                   |
| <b>Application Number:</b>                  | 15471506                                                   |
| <b>International Application Number:</b>    |                                                            |
| <b>Confirmation Number:</b>                 | 8014                                                       |
| <b>Title of Invention:</b>                  | USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS |
| <b>First Named Inventor/Applicant Name:</b> | George D. YANCOPOULOS                                      |
| <b>Customer Number:</b>                     | 96387                                                      |
| <b>Filer:</b>                               | Karl Bozicevic/Savanna Fuentes                             |
| <b>Filer Authorized By:</b>                 | Karl Bozicevic                                             |
| <b>Attorney Docket Number:</b>              | REGN-008CIPCON2                                            |
| <b>Receipt Date:</b>                        | 17-OCT-2018                                                |
| <b>Filing Date:</b>                         | 28-MAR-2017                                                |
| <b>Time Stamp:</b>                          | 12:36:26                                                   |
| <b>Application Type:</b>                    | Utility under 35 USC 111(a)                                |

### Payment information:

|                                                                                                                |                       |
|----------------------------------------------------------------------------------------------------------------|-----------------------|
| Submitted with Payment                                                                                         | yes                   |
| Payment Type                                                                                                   | CARD                  |
| Payment was successfully received in RAM                                                                       | \$ 1000               |
| RAM confirmation Number                                                                                        | 101718INTEFSW12362401 |
| Deposit Account                                                                                                |                       |
| Authorized User                                                                                                |                       |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: |                       |

| <b>File Listing:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                             |              |                                          |                  |                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|--------------|------------------------------------------|------------------|------------------|
| Document Number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Document Description        | File Name    | File Size(Bytes)/ Message Digest         | Multi Part /.zip | Pages (if appl.) |
| 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Issue Fee Payment (PTO-85B) | Web85b.pdf   | 46406                                    | no               | 2                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                             |              | 959c136ca5e68b9bd6e1c2d574dbd685d8e2440e |                  |                  |
| <b>Warnings:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                             |              |                                          |                  |                  |
| <b>Information:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                             |              |                                          |                  |                  |
| 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Fee Worksheet (SB06)        | fee-info.pdf | 31733                                    | no               | 2                |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                             |              | 57ecf70bfdbb182d88137b0655c4d86cd6fd16c8 |                  |                  |
| <b>Warnings:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                             |              |                                          |                  |                  |
| <b>Information:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                             |              |                                          |                  |                  |
| <b>Total Files Size (in bytes):</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                             |              | 78139                                    |                  |                  |
| <p><b>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</b></p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b><br/> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b><br/> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b><br/> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p> |                             |              |                                          |                  |                  |



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| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|------------|------------|---------------------|------------------|
| 15/471,506      | 11/20/2018 | 10130681   | REGN-008CIPCON2     | 8014             |

96387 7590 10/31/2018  
Regeneron - Bozicevic, Field & Francis  
201 REDWOOD SHORES PARKWAY  
SUITE 200  
REDWOOD CITY, CA 94065

## ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

### **Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)** (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

George D. YANCOPOULOS, Yorktown Heights, NY;  
REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

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