Study of COmparative Treatments for REtinal Vein Occlusion 2 [SCORE2]: a multicenter, prospective, randomized non-inferiority trial of eyes with macular edema secondary to central retinal vein occlusion, comparing intravitreal bevacizumab every 4 weeks with intravitreal aflibercept every 4 weeks.

Short title: Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2)
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Note: A separate SCORE2 Manual of Policies and Procedures (MOPP) developed to accompany this protocol will provide additional details and guidance on study operational activities. A Data Management Handbook (DMH) will provide details for data collection procedures and data quality management procedures. Participating sites will be provided the necessary instructions and review of the protocol, MOPP and DMH during site visits and/or at investigator meetings. The current master protocol (incorporating any approved amendments), MOPP, and DMH are always accessible to authorized study staff via the SCORE2 web page at www.score2crvo.com, where a username and password are required for access.
Précis

Macular edema is a major cause of vision loss in patients with central retinal vein occlusion (CRVO). The results of the Central Vein Occlusion Study (CVOS) showed that macular laser photocoagulation did not change the natural course of untreated macular edema associated with CRVO. However, recent advances have shown that pharmacotherapy with corticosteroids and molecules that inhibit the action of vascular endothelial growth factor (anti-VEGF) have a beneficial effect on the natural course of this disease. Currently, there are two corticosteroids (triamcinolone and the dexamethasone implant) and three anti-VEGF drugs (bevacizumab, ranibizumab and aflibercept) that are widely available to treat macular edema associated with CRVO. Each drug, individually, has been compared (most with level 1 evidence) with observation or a placebo and has been shown to have a robust effect on the disease. However, these drugs have not been compared directly against each other and there has not been guidance regarding which drug(s) may be used secondarily, as a rescue treatment, in cases where initial therapy is not successful. The Study of COmparative Treatments for RETinal Vein Occlusion 2 (SCORE2) will assess whether one of the most commonly used anti-VEGF drugs, bevacizumab, is non-inferior to a second generation anti-VEGF drug, aflibercept, for the treatment of macular edema secondary to CRVO. Rescue therapy, in cases where initial therapy is not successful, will also be evaluated.

SCORE2 is a multicenter, prospective, randomized, phase III clinical trial in which all participants enrolled will be followed for 12 months. SCORE2 is designed as a non-inferiority trial, with study eyes randomized to intravitreal bevacizumab (1.25 mg) every 4 weeks vs. intravitreal aflibercept (2.0 mg) every 4 weeks. SCORE2 aims to determine if bevacizumab is non-inferior to aflibercept for the treatment of macular edema associated with CRVO, with the primary outcome of visual acuity measured at Month 6. The non-inferiority margin is set at an Early Treatment Diabetic Retinopathy Study visual acuity letter score of 5 as measured by the electronic visual acuity test (E-ETDRS). For SCORE2, the sample size is 360 patients to be enrolled at up to 80 clinical sites. Following assessment of the primary outcome at Month 6, SCORE2 will use an adaptive treatment strategy in which participants with a good response who were initially assigned to aflibercept will be assigned randomly to one of two groups: 1) intravitreal aflibercept (2.0 mg) every 4 weeks (aflibercept q4); 2) intravitreal aflibercept (2.0
mg) using a treat and extend approach and those initially assigned to bevacizumab with a good response will be assigned randomly to one of two groups: 1) intravitreal bevacizumab (1.25 mg) every 4 weeks (bevacizumab q4); 2) intravitreal bevacizumab (1.25 mg) using a treat and extend approach. Study participants with a poor or marginal response at Month 6 in the aflibercept arm will receive rescue therapy with intravitreal dexamethasone. Study participants initially randomized to bevacizumab who have a poor response at Month 6 will receive aflibercept.
1. Introduction

The primary aim of the Study of COmparative Treatments for Retinal Vein Occlusion 2 (SCORE2) is to determine if bevacizumab is non-inferior to aflibercept for the treatment of macular edema associated with CRVO, with the primary outcome of visual acuity measured at 6 months.

Although corticosteroid therapy is a readily available treatment option, anti-VEGF therapy is most commonly used as initial treatment due to the perception that it is a more efficacious and safer therapy than corticosteroid therapy. Corticosteroid therapy is typically used as a rescue therapy for eyes that have an unsuccessful result with initial anti-VEGF therapy. Currently, several anti-VEGF treatment options to treat macular edema related to retinal vein occlusion are available, and there is uncertainty in the retina community as to which treatment to use initially and at what frequency. Bevacizumab and ranibizumab are closely related in molecular structure and in mechanism of action. These two drugs have also been demonstrated in a number of clinical trials for age-related macular degeneration (AMD) to have clinical equivalence. Aflibercept has a different molecular structure with a broader mechanism of action (in addition to antagonism of VEGF-A, there is antagonism of VEGF-B and placental derived growth factor). As a result of the related molecular structure of bevacizumab and ranibizumab and the similar clinical effects of these two drugs in AMD as well as a lack of a cost differential between ranibizumab and aflibercept, SCORE2 will directly compare bevacizumab with aflibercept. SCORE2 will assess whether bevacizumab is non-inferior to aflibercept (with the ability to test for superiority) for the treatment of decreased vision associated with macular edema secondary to CRVO. No comparative trial of bevacizumab vs. aflibercept for the treatment of CRVO has yet been conducted. From a public health perspective, it is important to be able to compare the efficacy and safety of these agents within the context of a single trial. In addition, there may be significant economic implications. Further, these agents are used frequently, typically every 4 weeks, and it is unclear whether such frequent treatment is needed to optimize visual acuity outcome and how long repeated treatments need to be administered. SCORE2 will not only compare these two treatments, but also will provide insight into dosing options after the initial 6 months to determine if the frequency of intravitreal injections can be reduced in eyes that have responded well to treatment (which would represent a more cost-effective treatment regimen,
with fewer risks to patients of injection-related adverse events and a lesser logistical treatment burden for patients and providers). The impact of rescue treatment will also be evaluated: intravitreal dexamethasone for eyes that have failed aflibercept, and aflibercept for eyes that have failed bevacizumab.

2. Background and Scientific Justification

Retinal vein occlusion (RVO) is the most common retinal vascular disorder after diabetic retinopathy. RVO affects 1-2% of the population older than 40 years\textsuperscript{1,2} and 16 million persons worldwide.\textsuperscript{3} Macular edema is the most frequent cause of vision loss in patients with RVO.\textsuperscript{4-6}

2.1. Previous CRVO Treatment Studies

Large-scale investigations for CRVO treatment began as early as the 1980s with the NEI-funded Central Vein Occlusion Study (CVOS), which evaluated the treatment of macular edema in CRVO with grid laser photocoagulation in 155 eyes (77 treated eyes and 78 control eyes) over a 3 year follow-up period.\textsuperscript{7} For untreated eyes with an initial visual acuity between 20/50 and 5/200 at presentation (n=78 eyes), 53 eyes were available for follow up at the 2 year visit. Of these eyes, 10 (19%) gained >2 lines of visual acuity at the 2 year follow up. Thirty-one eyes (59%) remained within one line of baseline visual acuity and 12 eyes (22%) lost >2 lines of visual acuity at the 2 year follow up. The final median visual acuity in untreated eyes was 20/160. The CVOS found no significant difference in visual outcome between the treatment and observation groups at any follow-up point.\textsuperscript{7} Thus, following publication of the CVOS results in 1993, patients with macular edema secondary to CRVO were generally observed or were treated with a variety of modalities without evidence-based guidance.

In 2003, the NEI funded another CRVO treatment study, the SCORE Study CRVO (SCORE-CRVO) trial, which demonstrated that intravitreal injection(s) of triamcinolone acetonide was superior to standard care established by the CVOS (i.e., observation) for vision loss associated with macular edema secondary to CRVO.\textsuperscript{8} In the SCORE-CRVO trial, the percentages of participants who achieved a gain in visual acuity letter score of $\geq 15$ from baseline to Month 12 were 27%, 26%, and 7% in the 1 mg, 4 mg, and observation groups, respectively. Although the SCORE-CRVO trial did demonstrate a visual acuity benefit for eyes treated with intravitreal triamcinolone compared with observation, among the eyes
treated with 1 mg intravitreal triamcinolone (the 1 mg group had a superior safety profile compared with the 4 mg group), 75% of eyes did not achieve a gain in visual acuity letter score of ≥15, the mean change in visual acuity from baseline to 12 months was a decrease of 1 letter, 28 eyes (34%) had 20/200 or worse visual acuity at 12 months, and only 25 (30%) eyes achieved a visual acuity at 12 months of 20/40 or better. Additionally, 50% of eyes still had center point thickness based on optical coherence tomography of >250 microns at 12 months. As a result, despite showing for the first time that a therapy could alter the natural course of macular edema secondary to CRVO in a beneficial way, the search for improvements in therapy continued.

The FDA approved Ozurdex (Allergan Pharmaceuticals, Inc., Irvine, CA), an intravitreal dexamethasone implant, for treatment of macular edema secondary to CRVO and branch retinal vein occlusion (BRVO) in 2009.9 However, it is not commonly used as a first-line therapy for CRVO-associated macular edema due to the perception that adverse events such as intraocular pressure (IOP) elevation and cataract are higher with the dexamethasone implant than with the anti-VEGF agents.9-14

At the same time that the SCORE Study results were published, results from industry-sponsored clinical trials evaluating ranibizumab for eyes with macular edema secondary to CRVO were presented and subsequently published. In the CRUISE Study, sponsored by Genentech (South San Francisco, CA), 392 patients with CRVO and macular edema were randomized to monthly intraocular injections of ranibizumab (an inhibitor of all isoforms of VEGF-A) or sham injections.10 At 6 months, the proportion of patients who gained ≥15 letters (3 lines) was 47.7% in the 0.5 mg ranibizumab group compared to 16.9% in the sham group (p<0.0001). Patients who received 0.5 mg ranibizumab gained a mean of 14.9 letters compared to a mean gain of 0.8 letters in the sham-treated patients (p<0.0001). FDA approval of ranibizumab for the treatment of CRVO-induced macular edema came in 2010. Similarly, there were numerous case reports and small randomized clinical trials of favorable visual acuity outcomes following intravitreal treatment with bevacizumab in patients with decreased vision associated with macular edema secondary to CRVO that were published.15-25 These reports concerning bevacizumab and the CRUISE Study results, combined with the
clinical perception that these drugs are possibly more efficacious and most likely safer (less cataract and IOP elevation) than corticosteroid therapy, allowed both bevacizumab and ranibizumab to rapidly become the first-line therapy over corticosteroids for CRVO eyes that have vision loss due to macular edema.

The newest anti-VEGF molecule, aflibercept, was approved by the FDA for wet AMD in February 2012 and then for CRVO on September 21, 2012. Aflibercept was recently studied in patients with macular edema due to CRVO in the COPERNICUS Study (sponsored by Regeneron Pharmaceuticals Inc. [Tarrytown, NY]), in which 189 patients were randomized 3:2 to receive 6 monthly injections of 2 mg aflibercept (previously known as VEGF Trap-eye) or sham. At 6 months, the proportion of patients who gained ≥15 letters was 56.1% in the aflibercept group compared with 12.3% in the sham group (p<0.0001). Patients who received aflibercept gained a mean of 17.3 letters compared to a mean loss of 4.0 letters in the sham-treated patients (p<0.001). In the GALILEO Study, sponsored by Bayer AG (Leverkusen, Germany), 172 patients were randomized 3:2 to receive 6 monthly injections of 2 mg aflibercept or sham. At 6 months, the proportion of patients who gained ≥15 letters was 60.2% in the aflibercept group compared with 22.1% in the sham group (p<0.0001). Patients who received aflibercept gained a mean of 18.0 letters compared with a mean gain of 3.3 letters in the sham-treated patients (p<0.0001). These results show a strong beneficial effect of aflibercept over the natural course of macular edema from CRVO and possibly a more beneficial effect than ranibizumab or bevacizumab when evaluating the percentage of 3-line gainers and the mean change in visual acuity from baseline. Although there may be theoretical benefits of aflibercept over ranibizumab and bevacizumab, there has been no formal comparison of bevacizumab to aflibercept in eyes with vision loss due to macular edema secondary to CRVO. This is particularly important given that bevacizumab was favored as the initial treatment for macular edema secondary to CRVO by over 60% of retina specialists surveyed in the 2013 American Society of Retina Specialists Preferences and Trends Survey.26

2.2. Significance of Comparing Anti-VEGF Agents for CRVO

Until recently, ranibizumab was the only anti-VEGF drug approved by the FDA for treatment of macular edema secondary to CRVO based on the CRUISE Study. More recently, based on
the results of the COPERNICUS and GALILEO studies, aflibercept was approved by the FDA for macular edema secondary to CRVO. Bevacizumab has been widely available for the treatment of macular edema secondary to CRVO since 2006. Currently, all 3 drugs are widely available and are reimbursed by 3rd party payors. If bevacizumab is demonstrated to be a non-inferior treatment to aflibercept in SCORE2, this would have important economic and public health implications. In SCORE2, only bevacizumab will be compared with aflibercept due to the similarities between bevacizumab and ranibizumab with regard to mechanism of action, as well as clinical trials which demonstrated clinical equivalence of bevacizumab and ranibizumab in AMD. Clinical equivalence of bevacizumab and ranibizumab for the treatment of wet AMD was demonstrated in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)\textsuperscript{14}, sponsored by the National Eye Institute, the Alternative Treatments to Inhibit VEGF in Age-related Choroidal Neovascularization (IVAN) Trial, sponsored by the National Institute for Health Research programme (United Kingdom)\textsuperscript{27,28} and the French Evaluation Group Avastin Versus Lucentis (GEFAL) Trial, sponsored by the Hospices Civils de Lyon\textsuperscript{29}.

2.3. Frequency of Anti-VEGF Treatment for CRVO and Rescue Therapies
In addition to the question of drug choice, these agents are typically used every 4 weeks, and there is uncertainty whether such frequent treatment is needed to optimize visual acuity outcome and how long repeated treatments need to be administered. SCORE2 will provide insight into treatment regimens after the initial 6 months to determine if the frequency of intravitreal injections can be reduced in eyes that have responded well to treatment (which would represent a more cost-effective treatment regimen, with fewer risks to patients of injection-related adverse events and a lesser logistical treatment burden for patients and providers), and the impact of alternative treatment strategies in eyes that have not responded well to initial treatment with anti-VEGF therapy.

3. Objectives
3.1. Primary Objective
The primary objective of SCORE2 is to test for non-inferiority based on mean change from baseline in visual acuity letter score at Month 6 for eyes randomized to intravitreal bevacizumab every 4 weeks compared with eyes randomized to intravitreal aflibercept every 4 weeks using a non-inferiority margin of 5 letters.
3.2. Secondary Objectives

Secondary objectives of SCORE2 are to:

- compare the bevacizumab and the aflibercept groups with regards to central retinal thickness, as measured with spectral domain optical coherence tomography (SD-OCT), at Month 6 and change between baseline and Month 6;
- assess Month 12 visual acuity and SD-OCT outcomes associated with different dosing strategies after Month 6 in participants who respond well to treatment;
- assess Month 12 visual acuity and SD-OCT outcomes associated with alternative treatment strategies after Month 6 in participants who respond poorly to treatment;
- compare area of retinal ischemia and rates of neovascular complications of CRVO in the bevacizumab vs. aflibercept groups;
- add to our knowledge of the safety profile of these anti-VEGF medications in the setting of eyes with macular edema secondary to CRVO;
- compare the bevacizumab and the aflibercept groups on vision-related quality of life as measured by the NEI VFQ-25;
- conduct a cost effectiveness analysis comparing intravitreal bevacizumab to intravitreal aflibercept to assess the economic implications from a payor perspective using decision analytic methods.

Other exploratory aims of SCORE2 are to:

- investigate the correlation of features identified through SD-OCT segmentation analysis, such as the IS-OS (inner segment-outer segment) junction (also known as the ellipsoid zone), with such characteristics as visual acuity and central retinal thickness;
- investigate the correlation of area of peripheral retinal nonperfusion from ultra-widefield fluorescein angiography with visual acuity and central retinal thickness, and the prognostic value of baseline peripheral and central retinal perfusion status in predicting disease course and treatment responsiveness;
- investigate the correlation of features on adaptive optics imaging with such characteristics as visual acuity and central retinal thickness.
4. Study Design and Methods

SCORE2 is a multicenter, randomized trial designed to test whether bevacizumab is non-inferior to aflibercept for the treatment of macular edema due to CRVO. Eligible participants will be randomized in a 1:1 ratio to:

1) intravitreal aflibercept (2 mg) every 4 weeks or
2) intravitreal bevacizumab (1.25 mg) every 4 weeks

The primary non-inferiority comparison between the 2 groups will be performed at Month 6. Participants assigned to aflibercept at baseline who meet the protocol defined criteria for a good response will be randomized to either continuing aflibercept every 4 weeks vs. changing to a treat and extend (TAE) regimen with monthly assessment. This will allow for an assessment of whether a TAE regimen can produce visual results similar to continued treatment every 4 weeks.

Participants assigned to bevacizumab at baseline who meet the protocol defined criteria for a good response will be randomized to either continuing bevacizumab every 4 weeks vs. changing to a TAE regimen. This will allow for an assessment of whether a TAE regimen can produce visual results similar to continued treatment every 4 weeks.

Participants originally assigned to bevacizumab with a protocol defined poor or marginal response at 6 months will receive aflibercept to determine whether a second generation anti-VEGF agent will be effective. Participants originally assigned to aflibercept with a protocol defined poor or marginal response at Month 6 will receive rescue therapy with a dexamethasone implant. Rescue therapy with bevacizumab for these patients is not part of the protocol since it is deemed more likely that participants who are failures to aflibercept, with its broad mechanism of action, will more likely respond to a dexamethasone implant.
The SCORE2 design is summarized in the following flow diagram:

**SCORE2 DESIGN**

- **Baseline**
  - aflibercept: monthly injections through Month 5
  - bevacizumab: monthly injections through Month 5

**Status assessment**
- at Month 6, when primary non-inferiority outcome is assessed

**Disposition after Month 6**
- Secondary outcomes measured at Month 12
  - aflibercept: monthly Months 6-11
  - aflibercept: TAE** Months b-11
  - dexamethasone implant at M6 and PRN at M9, M10, or M11
  - bevacizumab: monthly Months 6-11
  - bevacizumab: TAE** Months 6-11
  - aflibercept: monthly Months 6, 7, 8 and TAE**

**4.1. Efficacy Assessment**

**4.1.1. Primary Efficacy Outcome**

The primary efficacy outcome of this study is mean change in visual acuity letter score from the randomization visit to the Month 6 follow-up visit.

**4.1.2. Secondary Efficacy Outcomes**

Secondary efficacy outcomes include the following:

- Proportion of participants with improvement and proportion of participants with worsening by 15 or more in visual acuity letter score.

- Categorization of visual acuity for each study eye as:
  - improved (change from baseline \( \geq 5 \) or more letters),
  - stable (change from baseline between \(-4 \) and \(+4 \) letters), or
  - worse (change from baseline \( \leq -5 \) letters)

- Change in central subfield thickness, center point thickness, fluid status (including presence of intraretinal cystoid spaces and subretinal fluid) and macular volume as assessed by SD-OCT.

*Poor or marginal response: (1) Visual acuity letter score less than 58 (less than 20/80) OR visual acuity letter score improvement of 5 or less from baseline (i.e., Month 6 visual acuity letter score – Baseline visual acuity score \( \leq 5 \) letter). [Note that at least some of the visual acuity deficit is attributed, by the investigator, to macular edema secondary to CRVO] AND (2) OCT has one or more of the following: central subfield thickness of \( \geq 300 \) \( \mu \)m on SD-OCT (or \( \geq 320 \) \( \mu \)m if measured on Heidelberg Spectralis Machine), presence of intraretinal cystoid spaces, subretinal fluid.

**Good response: Otherwise**

**TAE = Treatment and extend with 2 week extension increments**
• Change from baseline in total score and sub-scales on vision-related quality of life as measured by the NEI VFQ-25 at Month 6 and at Month 12.

• Measurement of photoreceptor length, outer segment length, and integrity of the photoreceptor inner segment-outer segment (IS-OS) junction.

• Correlation of change in visual acuity letter score with retinal thickness outcomes at Month 6 and at Month 12.

• Correlation of change in visual acuity letter score with area of retinal ischemia.

### 4.2. Safety Assessments

#### 4.2.1. Major Safety Outcomes

Major safety outcomes include the following:

- Ocular (related to the injection or the drug): cataract, increased IOP (IOP exceeding 35 mm Hg while on maximal medical therapy), incisional surgery to lower IOP (e.g., filtration surgery, tube shunt surgery), infectious endophthalmitis, noninfectious endophthalmitis, retinal detachment, vitreous hemorrhage, and neovascular complications.

- Systemic: hypertension and arterial thromboembolic events defined by the Antiplatelet Trialists’ Collaboration.

### 4.3. Inclusion Criteria

#### 4.3.1. General Inclusion Criteria

a. Ability and willingness to provide informed consent.

b. Gender: Participants may be male or female.

c. Age: 18 years or older.

#### 4.3.2. Ocular Inclusion Criteria (Study Eye)

a. Participants must have center-involved macular edema secondary to CRVO. Eyes may be enrolled as early as the time of diagnosis of the macular edema. The definition of CRVO used in SCORE will also be used for the purposes of SCORE2: a CRVO is defined as an eye that has retinal hemorrhage or other biomicroscopic evidence of retinal vein occlusion (e.g., telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in all 4 quadrants.
b. Due to the similarities of a hemiretinal vein occlusion (HRVO) to CRVO, HRVO will be classified as CRVO for the purposes of this clinical trial. Eyes classified as having a HRVO will be limited to no more than 25% of the planned sample size. A HRVO is defined as an eye that has retinal hemorrhage or other biomicroscopic evidence of retinal vein occlusion (e.g., telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in 5 or more clock hours but less than all 4 quadrants. Typically, a HRVO is a retinal vein occlusion that involves 2 altitudinal quadrants.

c. E-ETDRS visual acuity score of greater than or equal to 19 letters (approximately 20/400) and less than or equal to 73 letters (approximately 20/40) by the ETDRS visual acuity protocol. The investigator must believe that a study eye with visual acuity between 19 and 33 letters is perfused.

d. Retinal thickness on SD-OCT measurement, defined as central subfield thickness of 300 μm or greater. If the SD-OCT measurement is taken from a Heidelberg Spectralis Machine, the central subfield thickness should be 320 μm or greater.

e. Media clarity, pupillary dilation and participant cooperation sufficient for adequate fundus photographs.

4.4. Exclusion Criteria

4.4.1. General Exclusion Criteria

Participants with any of the following conditions are ineligible:

a. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., chronic alcoholism or drug abuse, personality disorder or use of major tranquilizers indicating difficulty in long term follow-up, likelihood of survival of less than 12 months).

b. Participation in an investigational trial within 30 days of study entry that involved treatment with any drug that has not received regulatory approval at time of study entry.
c. History of allergy to any anti-VEGF agent, corticosteroid, or component of the delivery vehicle.

d. The participant will be moving out of the area of the clinical site to an area not covered by another clinical site during the 12 months of the study.

e. Positive urine pregnancy test: all women of childbearing potential (those who are pre-menopausal and not surgically sterilized) may participate only if they have a negative urine pregnancy test, and if they do not intend to become pregnant during the timeframe of the study. Women who are sexually active with a male partner must agree to use at least one of the following birth control methods: hormonal therapy such as oral, implantable or injectable chemical contraceptives; mechanical therapy such as spermicide in conjunction with a barrier such as a condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner.

f. Women who are breast-feeding.

4.4.2. Ocular Exclusion Criteria (Study Eye)

a. Examination evidence of vitreoretinal interface disease (e.g., vitreomacular traction, epiretinal membrane), either on clinical examination or OCT thought to be contributing to macular edema.

b. An eye that, in the investigator’s opinion, would not benefit from resolution of macular edema such as eyes with foveal atrophy, dense pigmentary changes or dense subfoveal hard exudates.

c. Presence of an ocular condition that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., age-related macular degeneration, uveitis or other ocular inflammatory disease, neovascular glaucoma, iris neovascularization, Irvine-Gass Syndrome, prior macula-off rhegmatogenous retinal detachment).

d. Presence of a substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by 3 lines or more (i.e., a 20/40 cataract).
e. History of laser photocoagulation for macular edema within 3 months prior to randomization.

f. History of intravitreal corticosteroid within 4 months of randomization.

g. Intravitreal anti-VEGF injection within 2 months of randomization. Note:

Enrollment will be limited to no more than 25% of the planned sample size with any history of anti-VEGF treatment. Once this number of eyes has been enrolled, any history of anti-VEGF treatment will be an exclusion criterion. For enrollment of study eyes with prior intravitreal anti-VEGF agents, in the opinion of the investigator, the treatment response to prior anti-VEGF treatment must be either incomplete or the study eye had developed recurrent CRVO-associated macular edema, such that the study eye would benefit from additional anti-VEGF treatment.

h. History of peribulbar or retrobulbar corticosteroid use for any reason within 2 months prior to randomization.

i. History of panretinal scatter photocoagulation (PRP) or sector laser photocoagulation within 3 months prior to randomization or anticipated within the next 3 months following randomization.

j. History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within 4 months prior to randomization or anticipated within the next 6 months following randomization.

k. History of YAG capsulotomy performed within 2 months prior to randomization.

l. Aphakia.

m. Presence of an anterior chamber intraocular lens.

n. Examination evidence of external ocular infection, including conjunctivitis, chalazion or significant blepharitis.

o. History of macular detachment.

4.5. Informed Consent, Screening Evaluation, and Randomization

4.5.1. Informed Consent

Potential participants in SCORE2 will be assessed as part of routine-care examinations. Prior to completing any procedures or collecting any data that are not part of usual medical care, written informed consent will be obtained. Data from procedures as part of usual medical care, which include the eye examination and an OCT, can be used in SCORE2, assuming they are done consistent with the protocol and within allowable timeframes. The informed consent should be reviewed with the patient at this visit and signed with the understanding that the patient may or may not be eligible. Consent may be given in two stages (if approved by the IRB), with one consent signature obtained prior to screening procedures specific to SCORE2 that are needed to assess eligibility. The second stage will be obtained prior to randomization and will be for participation in SCORE2. Thus, a single consent form will have two signature/date lines for the patient: one for the patient to consent to the screening procedures and one for the patient to consent for the randomized trial. Patients will be encouraged to discuss SCORE2 with family members and their personal physician(s) before deciding on study participation. Two identical consent forms are signed. One original consent form is to be kept in the participant’s study file and a second original is to be given to the participant to take home. The informed consent describes the study, randomization procedure, intravitreal treatment and participant responsibilities. Randomization will occur following confirmation of the patient’s eligibility for the study and decision to enter the study.

4.5.2. Screening Evaluation

a. An interview is conducted, including demographic information, medical history including ocular history, and current medications. This history is taken in order to ascertain whether there is any medical or ocular condition that may indicate ineligibility. The interview will also include smoking history and family history of CRVO or BRVO.

b. Visual acuity and manifest refraction (done within 8 days prior to randomization). Visual acuity testing and manifest refraction are performed using electronic ETDRS (E-ETDRS) visual acuity testing at 3 meters using the Electronic Visual Acuity Tester by a SCORE2 certified...
technician. This testing procedure has been validated against 4 meter standard ETDRS chart testing. Given the critical importance of visual acuity in this study, the best-corrected E-ETDRS visual acuity must be obtained in this very careful and standardized manner. Additionally, a “masked” visual acuity examiner with no knowledge of treatment assignments will perform visual acuity testing at the Month 6 and Month 12 visits. This “masked” examiner will be an individual not involved with the study except for the purpose of performing visual acuity testing. For example, this individual may be a clinic technician or a clinic coordinator for another clinical trial, but may not be the clinic coordinator for this trial.

c. IOP (done within 21 days prior to randomization). The IOP of both eyes will be measured prior to randomization.

d. Ophthalmic examination including dilated ophthalmoscopy (done within 21 days prior to randomization). The participant’s ocular status is evaluated by a study participating ophthalmologist for conditions that may make the participant ineligible as well as information necessary to complete the study forms. Lens assessment for cataract at the slit lamp will be performed with grading according to a modified Age-Related Eye Disease Study (AREDS) grading system.

e. Fundus photographs and spectral domain optical coherence tomography (SD-OCT) on the study eye only (done within 8 days prior to randomization). Good quality stereoscopic color fundus photographs (modified 3 fields of the study eye) and an SD-OCT measurement are required on the study eye for all participants. The SD-OCT measurement will be used to assess eligibility. These procedures are described in: University of Wisconsin-Madison Fundus Photograph Reading Center Fluorescein Angiography and Optical Coherence Tomography protocols.

f. Ultra-widefield fluorescein angiography will be performed on both eyes at selected sites (done within 21 days prior to randomization).
g. Quality of life assessment (NEI VFQ-25) *(done within 21 days prior to randomization).*

h. Blood pressure measurement *(done within 21 days prior to randomization).* Patients having elevated blood pressure should be referred to their primary care physician (PCP) for possible antihypertensive treatment / control; however, they may continue in the screening process.

i. Height measurement *(done within 21 days prior to randomization).*

j. Weight *(done within 21 days prior to randomization).*

k. For women of childbearing potential: Urine pregnancy test *(done within 8 days prior to randomization).*

4.5.3. Primary Randomization

A secure Internet-based eligibility, enrollment and randomization system is integrated into SCORE2. One eye of each participant will be randomly assigned to either treatment with bevacizumab q4 weeks or aflibercept q4 weeks. Treatment assignments, generated by the SCORE2 Data Coordinating Center, will be stratified according to the following baseline screening visual acuity groups: good visual acuity (73-59 letters: 20/40 to 20/63), moderate visual acuity (58-49 letters: 20/80 to 20/100), and poor visual acuity (48-19 letters: 20/125-20/400). In participants with both eyes eligible, the eye to be randomized into SCORE2 will be at the discretion of the physician and patient. Secondary randomizations (without stratification) will occur at 6 months within the good-responders group in either primary arm that will assign these participants to continued therapy at either a q4 weeks or a TAE dosing schedule.

4.6. Study Drug Formulations and Intravitreal Injection Procedures

Regeneron Pharmaceuticals Inc. (Tarrytown, NY) will be providing aflibercept to be used in SCORE2. The physical, chemical, and pharmaceutical properties are detailed in the aflibercept package insert (Appendix 2). Bevacizumab will be aliquoted, labeled and shipped by a centralized compounding pharmacy. The physical, chemical and pharmaceutical properties of the study drug and formulation are detailed in the Clinical Investigator’s Brochure (Appendix 3). Dexamethasone, when needed by poor responders during the second
portion of the trial, will be provided by Allergan (Irvine, CA). The physical, chemical, and pharmaceutical properties are detailed in the dexamethasone package insert (Appendix 4).

The full injection procedure for aflibercept, bevacizumab, and dexamethasone is described in the SCORE2 MOPP. The same technique is followed for the both initial treatments and retreatments.

4.7. Participant Visit Schedule, Masking, Retreatment, Rescue Treatment and Other Treatments

4.7.1. Visit Schedule

Appendix 1 shows the follow-up visit schedule for all participants through Month 12. For all eyes, follow-up visits will be every 4 weeks for the duration of the 12-month study. At each study follow-up visit, E-ETDRS visual acuity, IOP measurement, and ophthalmic examination will be performed. SD-OCT of the study eye will be performed at each study visit. Manifest refraction will be performed at baseline and at Months 6 and 12. Modified three-field fundus photography of the study eye will be performed at baseline and at Months 6 and 12. Ultra-widefield fluorescein angiography and adaptive optics will be performed on both eyes at selected sites at baseline and at Months 6 and 12. The NEI VFQ-25 quality of life assessment will be performed at baseline and at Month 6 and 12. A negative urine pregnancy test must be obtained from all women of childbearing potential during the screening process and prior to each study injection. Assessment of ocular symptoms or ocular problems other than for macular edema or the follow-up of adverse events may require additional visits. These supplemental visits are to be scheduled promptly at the investigator’s discretion.

4.7.2. Testing Procedures to be Performed at Follow-up Visits (see Appendix 1)

The following procedures will be performed at each follow-up visit on both eyes unless otherwise specified.

1. E-ETDRS visual acuity in each eye. Manifest refraction will be performed at Months 6 and 12. At other visits, the need for a refraction is determined by the investigator based on usual care considerations. A refraction should be performed when there is a change in visual acuity of 15 or more letters (better or worse) from the visual acuity score at the time of the last refraction.
2. IOP measurement in each eye.

3. Ophthalmic examination, including a dilated fundus examination and a slit-lamp examination, on both eyes.

4. Fundus photography. Modified three field fundus photography will be performed on the study eye at Months 6 and 12.

5. SD-OCT on the study eye at each study visit. The SD-OCT must be performed by a masked technician at Months 6 and 12.

6. Lens assessment on the study eye, using modified AREDS standard lens photographs, for cataract will be performed by the investigator at Months 6 and 12.

7. Blood pressure measurements will be performed at Months 6 and 12. Patients having elevated blood pressure should be referred to their primary care physician (PCP) for possible antihypertensive treatment / control.

8. The NEI VFQ-25 quality of life assessment will be performed at Month 6 and 12.

9. Urine pregnancy test on all women of child-bearing potential prior to the study injection.

10. Ultra-widefield fluorescein angiography will be performed on both eyes at selected sites at Months 6 and 12. Axial length measurement will be requested on the study eye.

11. Adaptive optics will be performed on both eyes at selected sites after the randomization visit but prior to the Month 1 visit and at Months 6 and 12.

At unscheduled visits, the procedures performed will be determined by the investigator.

4.7.3. Termination of Injections Due to Pregnancy

All female study participants of child-bearing potential must have a negative pregnancy test prior to each study injection. In the event of a pregnancy, study injections must be terminated.

4.7.4. Secondary Randomization

At the 6-month visit, the primary outcome is determined. At 6 months, study eyes will be categorized into one of two groups based on response to treatment:
Poor or marginal response:

Visual acuity letter score less than 58 letters (less than 20/80) OR visual acuity letter score improvement of 5 or less from baseline (i.e., Month 6 visual acuity letter score – Baseline visual acuity letter score ≤ 5 letters).

Note that at least some of the visual acuity deficit is attributed, by the investigator, to macular edema secondary to CRVO and OCT has one or more of the following: OCT thickness (defined as central subfield thickness of 300 μm or greater. If the SD-OCT measurement is taken from a Heidelberg Spectralis Machine, the central subfield thickness should be 320 μm or greater), presence of intraretinal cystoid spaces, subretinal fluid.

Good response: Otherwise

For the study eyes with a good response, a secondary 1:1 randomization takes place with the assignment to continued q4 week treatment vs. a treat and extend regimen as described below. For the study eyes with a poor or marginal response alternative treatment will be provided as described below.

4.7.5. Retreatment at or After Month 6 in Good Responders: Q4 Weeks or Treat and Extend (TAE) Regimen

Study eyes with a good response randomized to monthly injections will receive six q4 week injections from Month 6 to Month 11, with treatment based on the original treatment assignment (i.e., either aflibercept or bevacizumab).

Study eyes with a good response randomized to either aflibercept TAE (Months 6-11) or bevacizumab TAE (Months 6-11) will receive an injection at Month 6, and then those eyes without persistent thickness (note: persistent thickness is defined as central subfield thickness of 300 μm or greater on OCT; however, if the SD-OCT measurement is taken from a Heidelberg Spectralis Machine, the central subfield thickness should be 320 μm or greater), intraretinal cystoid spaces (on OCT), or subretinal fluid (on OCT) will have subsequent visits extended out to a visit interval 2 weeks longer than the prior interval. For example, if an eye is without persistent thickness, intraretinal cystoid spaces, or...
subretinal fluid and is being evaluated at a 6 week interval, treatment is provided and the next visit will be at 8 weeks. Visits can be extended out to a maximum of 10 weeks. In contrast, eyes with any persistent thickness, intraretinal cystoid spaces, or subretinal fluid are retreated and must be brought back in 4 weeks. The following figure provides details on the criteria for implementing the TAE regimen.

**OCT Findings**
Any of the following present?
1) Persistent thickness
2) Intraretinal cystoid spaces
3) Subretinal fluid

**Yes**
Injection and follow-up in 4 weeks

**No**
Injection and extend follow-up for 2 additional weeks

### 4.7.6. Rescue Treatment
Study eyes with a poor or marginal response will receive rescue therapy. Secondary outcomes will be measured at 12 Months.

- Eyes in the aflibercept arm will receive dexamethasone treatment at Month 6 and then PRN at Month 9, 10 or 11. Dexamethasone treatment will be given at Month 9 if there is evidence of persistent thickness (defined as central subfield thickness of 300 μm or greater on OCT; however, if the SD-OCT measurement is taken from a Heidelberg Spectralis Machine, the central subfield thickness should be 320 μm or greater), intraretinal cystoid spaces (on OCT), or subretinal fluid (on OCT). If treatment is not given at Month 9, dexamethasone treatment can also be given at Month 10 or Month 11 (if not given at Month 10) if there is evidence of persistent thickness, intraretinal cystoid spaces, or subretinal fluid at Month 10 or Month 11 (if not given at Month 10). Note: study eyes with IOP of 25 mm Hg or higher that are scheduled to receive dexamethasone should have treatment delayed until the IOP is controlled (i.e., less than 25 mmHg). Further, study eyes
meeting the criteria to receive dexamethasone will also be assessed for contraindications listed in the dexamethasone package insert, which include ocular or periocular infections, advanced glaucoma, aphakia with rupture of posterior lens capsule, and hypersensitivity. If dexamethasone treatment is contraindicated based on any of these criteria, bevacizumab treatment with the SCORE2 drug formulation will be used at Months 6, 7, and 8 and then on a TAE regimen.

- Eyes in the bevacizumab arm will receive aflibercept at Months 6, 7, 8 and then on a TAE regimen.

### 4.7.7. Masking

Visual acuity testers and OCT technicians will be masked to treatment group at the 6-month and 12-month visits.

**Primary randomization:** All study participants will be masked to their original treatment assignment through Month 6. The investigators and the clinic coordinators will not be masked to the original treatment group assignment.

**Secondary randomization (good responders):** From Month 6 to Month 12, participants will continue to be masked to study drug. However, masking the participant to the dosing schedule (i.e., monthly vs. TAE) in the secondary randomization groups from Month 6 to Month 12 is not possible due to the varying visit schedules. The investigators and coordinators will not be masked.

**Secondary randomization (poor or marginal responders):** From Month 6 to Month 12, masking the participant is not possible due to the differences in the dexamethasone implant and aflibercept injections and the varying visit schedules. The investigators and coordinators will not be masked.

### 4.7.8. Other Treatments

If, in the investigator’s judgment, the study eye requires additional treatment other than prescribed by the randomized assignment, then the Study Chair or Co-Chair should be contacted to discuss possible treatments.
4.7.9. Fellow Eye Treatments
To keep participants exposed to only one anti-VEGF drug during the course of the study, the fellow eye, in the event it requires treatment with anti-VEGF therapy, should be treated with the same anti-VEGF drug as the study eye. Should the fellow eye require treatment with aflibercept, then aflibercept will be provided by SCORE2. In the cases where bevacizumab eyes are switched (per protocol) to aflibercept, treatment of the fellow eye will be at the discretion of the investigator.

4.8. Diagnosis and Treatment of Safety Events

4.8.1. Endophthalmitis Treatment
The decision to treat a patient for an endophthalmitis or a suspected endophthalmitis will be guided by the clinical judgment of the investigator. The treatment method (pars plana vitrectomy vs. vitreous tap) and choice of antimicrobial agents is also at the discretion of the investigator and should follow current standard practice patterns. The decision to use intravitreal steroids (e.g., dexamethasone) for the treatment of endophthalmitis is also at the discretion of the investigator.

4.8.2. Treatment of Elevated Intraocular Pressure (IOP)
The decision to treat a study participant for elevated IOP will be guided by the clinical judgment of the investigator. The treatment to prescribe will be at the discretion of the investigator and may include referral to another ophthalmologist.

4.8.3. Cataract Surgery
It is expected that some study participants will develop cataract within the study period. The decision to perform cataract surgery is at the discretion of the investigator and the patient. Indications for cataract surgery should follow guidelines developed by the American Academy of Ophthalmology, Preferred Practice Pattern (Cataract in the Adult Eye, 2011, page 14).

4.8.4. Surgery for Proliferative Retinopathy and Other Complications Due to Retinal Vein Occlusion
It is expected that some study participants will develop vitreous hemorrhage and/or other complications of retinal vein occlusion that may cause visual impairment. Vitrectomy for the complications of proliferative retinopathy such as vitreous hemorrhage should be delayed, if clinically feasible, because vitreous hemorrhage may resolve, obviating the
need for vitrectomy.

A suggested treatment plan that may be followed for eyes with vitreous hemorrhage and/or other complications of retinal vein occlusion is as follows:

1. Eyes with visually significant, non-clearing vitreous hemorrhage should have vitrectomy performed if there is no significant clearing in 3 months.
2. Eyes with traction retinal detachment involving or threatening the fovea should have vitrectomy performed as soon as clinically indicated.
3. Eyes with a combined traction-rhegmatogenous retinal detachment should have vitrectomy performed as soon as clinically indicated.
4. Eyes with extensive and progressive fibrovascular proliferation should have vitrectomy performed as soon as clinically indicated.
5. Eyes with vitreoretinal interface disease such as from vitreomacular traction or an epiretinal membrane can, at the discretion of the investigator, have vitrectomy performed if the investigator believes that the primary cause of macular edema and reduced visual acuity is due to the vitreoretinal interface disease.

4.9. Genetic Biorepository

4.9.1. Background

SCORE2 will collect saliva samples from study participants to be placed in a genetic biorepository to serve as a future resource to study genes related to eye disease and possibly other diseases. For example, possible investigations from future use of the samples will be to compare to a control population to explore genetic risk factors for CRVO, if suitably matched controls are available. Further, it is expected that some patients may respond poorly or will not respond to anti-VEGF therapy, or conversely, respond better than expected. Future use of these samples may allow the opportunity to identify genetic factors that may be related to response status from the anti-VEGF agents.

The results of the future research studies may help researchers find new ways to prevent, detect, and treat health problems in the future and may help educate doctors in training.
4.9.2. Specimen Collection Procedures

4.9.2.1. Eligibility

All study participants from participating SCORE2 sites who have consented and are randomized into SCORE2 will be provided an opportunity to provide a saliva specimen for the genetic biorepository.

4.9.2.2. Informed Consent

SCORE2 participants will be approached to contribute a saliva specimen by physicians or authorized representatives familiar with the genetic biorepository. Prior to providing the saliva specimen, a signed informed consent will be collected. This consent may be requested at the time of the main study consent, or after the main consent, based on the site’s IRB requirements. If an IRB does not approve a consent form for the collection of the saliva specimen at a particular site, SCORE2 participants at that site will not be asked to provide a saliva specimen. Note that only SCORE2 participants who have been randomized will be requested to provide a saliva sample. If there is a problem in preparing the saliva specimen obtained from the participant for storage, another specimen may be requested.

Providing a saliva sample for the genetic biorepository for future use is voluntary, and a participant may choose to participate in SCORE2 while not providing a saliva specimen for the biorepository. There will not be any threat of adverse consequences if the study participant does not agree to provide a saliva sample. Participants may request to have their sample withdrawn at any time before samples are released by Penn State Institute for Personalized Medicine (IPM) to researchers by informing the clinical site of their request. As soon as the withdrawal request is received, the IPM BioRepository will destroy the sample. The IPM BioRepository will not be able to withdraw or destroy any samples that have already been distributed to research scientists.

4.9.2.3. Saliva Samples

Participants will be requested to spit into a small tube or container for storage. Saliva samples will be collected at the clinical sites using commercial kits (Oragene/DNA Genotek) and mailed directly from the clinical site to IPM.
4.9.2.4. **Saliva Sample Processing and Storage**

The saliva samples will be processed and banked by IPM BioRepository personnel. Samples will be stored indefinitely except in those cases where a participant requests that their sample be withdrawn.

4.9.2.5. **Vial Labeling and Sample Preparation**

All samples will be labeled with a unique identifier. No PHI will be placed on the biosample storage vials/tubes/containers. The saliva will be aliquoted into storage tubes, labeled, and stored at –80°C.

4.9.3. **Donor Privacy and Confidentiality**

The IPM BioRepository will take measures to protect participant privacy. Identifiable information will not be collected by IPM. The IPM BioRepository will not accept or store any personally identifying information on the sample submitted and, therefore, both submitters and withdrawers of samples are HIPAA compliant during biorepository usage. A de-identified data set will be created by the SCORE2 DCC and will include information collected as part of the study, including medical and ocular history, and treatment and ocular information collected after randomization. These data will be maintained at the SCORE2 DCC and not stored at the IPM BioRepository.

4.9.4. **Distribution of Samples**

A SCORE2 Ancillary Studies Access Committee will provide access to SCORE2 samples and data for ancillary studies and will be the primary steward of these resources. The SCORE2 Ancillary Studies Access Committee will review and approve all uses of samples and data. The SCORE2 Ancillary Studies Access Committee will consist of the SCORE2 Executive Committee during the funding of SCORE2, and a committee will be convened by the DCC if the requests occur after SCORE2 funding has ended. All requests must be prepared in writing and provide a concise, scientific summary of the project goals and objectives (1 page single-spaced limit), number of samples requested, statistical power estimates, analytical procedures proposed, qualifications of the requestors to meet scientific goals, and evidence of funding to carry out the research. The request must also be accompanied by an assurance form signed by an official of their organization. Once approved by the SCORE2 Ancillary Studies Access Committee,
samples will be mailed to study investigators by the Penn State Hershey IPM BioRepository personnel and de-identified phenotypic data will be distributed by the SCORE2 DCC.

5. Data Monitoring and Adverse Event Reporting

5.1. Data and Safety Monitoring Committee

The SCORE2 Data and Safety Monitoring Committee (DSMC) is responsible for reviewing the study design and, as appropriate, recommending design changes to the SCORE2 Executive Committee and the NEI. The DSMC also may recommend to the NEI to suspend enrollment if adverse events predominate. In addition, the DSMC assesses study data, particularly for adverse and/or beneficial effects of treatment. The DSMC is expected to meet approximately every six months and will review all accumulating study data including adverse events.

5.2. Methods and Timing for Assessing, Recording and Analyzing Safety Parameters

Each clinical site is responsible for reporting all adverse events, including toxicities, which occur to SCORE2 participants enrolled at their site, regardless of relatedness to study therapy or procedure. All safety events are reported from the time of consent through the last study visit. Reporting of all adverse event data is expected within 7 days of recognition.

Serious adverse events (SAEs), as defined in Section 5.3.1.2 must be reported to the SCORE2 DCC within 24 hours of recognition by the site. Study investigators must report serious adverse events promptly in accordance with regulations to their local ethics review committee (or IRB) or the central IRB, as applicable, in addition to the SCORE2 DCC.

5.3. Procedures for Reporting Adverse Events

All adverse events will be entered into the data system within 7 days of identification. All serious events will be entered into the data system within 24 hours of identification. If there are technical difficulties of entering the event into the electronic data capture (EDC) system, the SAE will be reported to the DCC by fax communication. All information reported by fax will need to be entered in the data system when it is available.
The assigned SCORE2 Coordinating Center staff may be contacted at the DCC, The Emmes Corporation, located in Rockville, Maryland. Back-up personnel and procedures are in place to ensure appropriate handling of urgent requests or questions regarding adverse event reporting requirements.

The Emmes Corporation
Fax +1 888-440-0561
score2-safety@emmes.com

Any serious adverse event entered in the EDC system will generate an automatic email notification to the DCC and the IND sponsor. The DCC Medical Monitor will review each SAE and will determine whether the SAE meets the criteria for expedited reporting. The final decision for disposition regarding expedited reporting to the FDA rests with the IND sponsor or its designee.

The investigator or designee is responsible for reporting all SAEs to local Institutional Review Boards/Ethic Committees (IRBs/ECs) per local IRB/EC requirements or the central IRB, as applicable.

### 5.3.1. Expedited Reporting

All serious and unexpected suspected adverse reactions are reported to the FDA in writing within 15 calendar days of notification. Suspected adverse reactions that are unexpected and meet the criteria for death or immediately life-threatening also require notification of the FDA as soon as possible but no later than 7 calendar days of notification of the event, with a follow-up written report within 15 calendar days of notification of the event.

For any event determined to require expedited reporting, the DCC will prepare an expedited report (MedWatch Form FDA 3500A or similar) and forward it to the IND sponsor or its designee for regulatory submission. The IND sponsor or its designee will notify the FDA (and other relevant regulatory authorities), while the DCC will notify the DSMC, the central IRB, and all participating investigators. The investigator will forward a copy of all expedited reports to their local IRB/EC local IRB/EC requirements.
5.3.2. **Definition of Adverse Event**

An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

5.3.2.1. **Suspected Adverse Reaction**

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by the drug.

5.3.2.2. **Unexpected Adverse Events**

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the study drug investigator brochure and package insert, as applicable, or is not listed at the specificity or severity that has been observed.

5.3.2.3. **Serious Adverse Events (SAE)**

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
5.3.2.4. Relation of AE to Study Drug or Intravitreal Injection

The physician acting as the Principal Investigator at each study site or his/her physician designee should make the determination of relatedness of an adverse experience to the study drug or the intravitreal injection. The relatedness determination should be made for every adverse event, regardless of severity or event type (routine AE or SAE). A causal relationship is present if there is a reasonable possibility that the study drug or the intravitreal injection caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study drug or the intravitreal injection and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a study drug or the intravitreal injection.

5.3.3. Criteria for Grading Adverse Events

The severity of an adverse event is determined by the investigator by using the following definitions:

5.3.3.1. Grade 1—Mild

Participant is aware of symptoms or has minor findings but tolerates them well and no or minimal intervention required.

5.3.3.2. Grade 2—Moderate

Participant experiences enough symptoms or findings to require intervention.

5.3.3.3. Grade 3—Severe

Participant experiences symptoms or findings that require significant intervention.

5.3.3.4. Grade 4—Life-Threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
5.3.3.5. Grade 5—Death

5.4. Procedure for Reporting of Pregnancy

Pregnancy, per se is not regarded as an adverse event. Any pregnancy that occurs while the participant is enrolled in the study will be captured on a pregnancy CRF and not separately reported as an AE or SAE. The investigator should report the pregnancy to the DCC by entering it in EDC within 24 hours of its identification. Women who become pregnant during the study will not receive further injections, but may continue follow-up with monthly visits if they are willing to do so. They will be referred for medical care, and the pregnancy is followed until an outcome is known (i.e., spontaneous miscarriage, elective termination, normal birth or congenital anomaly). All reports of congenital anomalies/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study. Elective abortion procedures, without complications, should not be considered as adverse events. All live births must be followed for a minimum of 30 days or to the first well-baby visit.

6. Statistical Considerations


6.1.1. Primary Efficacy Outcome Measure and Time Point

The primary efficacy outcome of this study is mean change in visual acuity letter score from the randomization visit to the 6-month follow-up visit. The primary analysis is based on observed data at 6 months, and analyzes participants based on the arm to which they are randomized (consistent with intent-to-treat principles). In our primary and important secondary analyses, we plan to assume that data are missing at random (MAR), so that conventional likelihood statistics ignoring the missing observations are optimal. Secondary analyses will explore the sensitivity of the conclusions to departures from MAR.

6.1.1.1. Primary Efficacy Analysis Method

The non-inferiority test is carried out by modeling baseline and 6-month visual acuity data for each patient in the primary analysis as a two-step AR(1) process as follows:

\[
\begin{bmatrix}
Y_0 \\
Y_1
\end{bmatrix}_i = \alpha \begin{bmatrix} 1 \\ 0 \end{bmatrix} + \gamma \begin{bmatrix} 0 \\ 1 \end{bmatrix} + \beta \begin{bmatrix} 0 \\ \epsilon_1 \end{bmatrix}_i
\]

where
\( Y_i \) and \( Y_{1i} \) are the visual acuities of the \( i \)th individual at baseline and 6 months, respectively.

- \( \alpha \) is the mean baseline visual acuity, assumed because of randomization to be the same in both arms.
- \( \gamma \) is the time (=visit) effect.
- \( T_i \) is the treatment (bevacizumab) indicator for the \( i \)th individual.
- \( \beta \) is the treatment effect.
- \( E(\epsilon) = 0 \) and \( V(\epsilon) = \sigma^2 \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix} \).

We use the AR(1) approach instead of the conceptually simpler ANOVA, which compares arms with respect to changes from baseline, because the AR(1) model offers better power under circumstances consistent with the design of SCORE2. In this model, the non-inferiority test involves testing the null hypothesis of \( \beta \leq -M \) vs. the alternative of \( \beta > -M \), where \( M = 5 \), the non-inferiority margin.

### 6.2. Assumptions for and Result of Sample Size Estimation

The primary hypothesis of SCORE2 is that, with respect to changes from baseline in visual acuity letter score, bevacizumab (the test drug T) is not inferior to aflibercept (the active control C), where non-inferiority is defined using a 5-letter non-inferiority (NI) margin. The FDA guidance for industry Non-Inferiority Clinical Trials\(^{31}\) provides guidance on selecting a NI margin. A NI study seeks to show that the difference in response between the active control (C) and the test drug (T), (C-T), the amount by which the control is superior to test drug, is less than some pre-specified non-inferiority margin (M). M can be no larger than the presumed entire effect of the active control in the NI study (that is, the presumed difference between active control and placebo), and the margin based on that whole active control effect is generally referred to as M1. What is the entire effect of the active control (aflibercept) assumed to be present in SCORE2? The COPERNICUS trial, sponsored by Regeneron Pharmaceuticals Inc., and the GALILEO trial, sponsored by Bayer HealthCare, both compared aflibercept to sham injection and therefore provide data on the active control effect. In COPERNICUS, the difference (aflibercept-sham) in mean change from baseline in visual acuity letter score (M1) was 21.7 (95% Confidence Limits: 17.4, 26.0). In GALILEO, the difference (aflibercept-sham) in mean change from baseline in visual acuity letter score...
(M1) was a little smaller, at 14.7 (95% Confidence Limits: 10.8, 18.7). [Personal communication, Regeneron Pharmaceuticals].

Per discussions with FDA, an acceptable NI margin is one that is less than half of the lower end of the 95% confidence interval of the active control effect (i.e., the difference between aflibercept and placebo). A margin of 5 letters based on data from the COPERNICUS and GALILEO trials meets this definition suggested by the FDA, and is used for SCORE2. Knowledge of the variability in the outcome measure of change from baseline in visual acuity letter score is also necessary for the sample size calculations. We selected a standard deviation (SD) of 16, which is consistent with what was reported by the CRUISE study\textsuperscript{10} for change from baseline in visual acuity letter score (SD=15.9 based on 0.3 mg Lucentis arm). This estimate is higher than observed in the COPERNICUS (SD=12.8) and GALILEO (SD=12.2) trials, however we chose to be conservative in our sample size calculations by choosing a higher SD, with building in a sample size re-estimation plan into the SCORE2 design to estimate the SD partially through the trial and re-estimate sample size accordingly.

Table 1 shows the total sample size required for 80% and 90% power to test this non-inferiority hypothesis at level 0.05 two-tailed, assuming the standard deviation is 16, and 10% attrition by 6 months. The planned sample size of 360 suffices for 80% power with a non-inferiority margin of 5 letters.

<table>
<thead>
<tr>
<th>Non-inferiority Margin</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80%</td>
</tr>
<tr>
<td>5.5 letters</td>
<td>296</td>
</tr>
<tr>
<td>5 letters</td>
<td>358</td>
</tr>
<tr>
<td>4.5 letters</td>
<td>442</td>
</tr>
</tbody>
</table>

Important secondary outcomes involve visual acuity letter score changes from Month 6 to Month 12. The secondary findings are generalizable only to participants who were not lost
during the initial 6 months. Among good responders within each of the primary arms (aflibercept vs. bevacizumab), we compare the visual acuity letter score changes in the monthly vs. TAE sub-arms formed by the secondary randomizations at 6 months. Among poor responders in both arms, we describe visual acuity changes between Month 6 to Month 12 after receiving dexamethasone or aflibercept (monthly), although the value of this description is limited by the lack of a comparator group. To explore the effects upon the secondary analyses of attrition and subdivision of the original sample sizes, we performed a simulation in which we assumed that the attrition would be 10% during each of the two periods (baseline to Month 6, Month 6 to Month 12), that 75% of the non-lost-to-followup responses would be good and 25% poor in both primary arms, and that the visual acuity changes during the second Month 6 to Month 12 period would have a standard deviation of 16, independent of the changes in the previous period. Note that 75% good response rate is a conservative estimate, as 85% of the aflibercept participants in the COPERNICUS trial experienced a >5 letter improvement over baseline in visual acuity at 6 months (personal communication from Regeneron Pharmaceuticals) and 80% of Lucentis (0.3 mg) eyes experienced a >5 letter improvement in visual acuity at 6 months. Also, the 10% attrition rate for each 6-month time period through is consistent with the SCORE-CRVO trial, which had 94% retention at Month 4, 87% at Month 8, and 88% at Month 12. Under these assumptions, the resulting 95% confidence intervals about the secondary outcomes will have half-widths as described in Table 2. Note that a full accounting of participant flow with sample sizes is provided in the SCORE2 MOPP.

Table 2. 95% Confidence Interval Half-widths (changes in visual acuity letter score) for Secondary Outcomes

<table>
<thead>
<tr>
<th>Type of CI of VA change from Month 6 to Month 12</th>
<th>Mean</th>
<th>95th %tile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference between every 4 week and TAE groups of good responders</td>
<td>6.06</td>
<td>6.84</td>
</tr>
<tr>
<td>Poor responders in either arm</td>
<td>5.39</td>
<td>6.82</td>
</tr>
</tbody>
</table>

Table 2 shows that, under the assumptions of the simulation, the confidence interval half-width for any of the secondary comparisons is less than 7 letters. If the rates of loss/refusal of secondary randomization, or of response at 6 months, differ from the assumptions of the
simulation, the expected numbers of participants will change. In particular, if one primary arm proves superior to the other, the rates of good vs. poor outcomes will not be the same in the two arms. Also, if participants who are good responders at 6 months refuse randomization, opting instead to continue with the therapy that has proven successful for them, the expected number of participants available at the secondary randomizations will change. Although the estimates for the secondary outcomes have fairly wide confidence interval half-widths based on the expected sample sizes at Month 12, these results will provide useful information for CRVO patient management with respect to treatment, and provide data to help design subsequent CRVO treatment trials.

6.3. Safety Outcomes

Key ocular safety variables to be analyzed are:

1. **Ocular (related to the injection or the drug):** cataract, increased IOP (IOP exceeding 35 mm Hg while on maximal medical therapy), filtration surgery to lower IOP, infectious endophthalmitis, noninfectious endophthalmitis, retinal detachment, vitreous hemorrhage, new-onset retinal arterial occlusion and neovascular events.

2. **Systemic:** hypertension and arterial thromboembolic events defined by the Antiplatelet Trialists’ Collaboration.

6.4. Secondary Efficacy Outcomes

Group differences in changes in visual acuity letter score from baseline to Month 6 will be analyzed between the two primary treatment groups and between the secondary randomized groups (between Month 6 and Month 12) to investigate the following:

- Proportion with improvement or worsening by 15 or more in visual acuity letter score
- Longitudinal analysis examining mean change from baseline to each month visit in visual acuity letter score
- Categorization of each participant as:
  - improved (change from baseline ≥+5 or more letters),
  - stable (change from baseline between −4 and +4 letters), or
  - worse (change from baseline ≤−5 letters)

Important secondary efficacy outcomes related to retinal thickness outcomes between treatment groups within the primary randomized groups and then separately between
treatment groups, where applicable, within secondary randomized groups will be examined. These include:

- Central subfield, center point thickness, macular volume, and extent of cystoid space as assessed by SD-OCT.
- Percent change from baseline in calculated retinal thickness at the center of the macula.
- Area of retinal thickness and hemorrhage as assessed by stereoscopic color fundus photography.
- Measurement of photoreceptor length, outer segment length, and integrity of the photoreceptor inner segment-outer segment (IS-OS) junction via SD-OCT segmentation analysis.
- Correlation of change in visual acuity letter score with retinal thickness at Month 6 and at Month 12.
- Relationship between early (Month 1, 2, and 3) and Month 6 retinal fluid status, defined as central subfield thickness of 300 μm or greater (or 320 or greater on Heidelberg Spectralis Machine) and either presence of intraretinal cystoid spaces or subretinal fluid, and the outcomes of number of intravitreal injections given and visual acuity letter score over time.

Other important secondary efficacy outcomes examining the relationship of the efficacy outcomes measured from ultra-widefield fluorescein angiography and AO assessments and other outcomes within exploratory analyses including:

- Correlation of area of peripheral retinal nonperfusion with visual acuity and central retinal thickness, and the prognostic value of baseline peripheral and central retina perfusion status in predicting disease course and treatment responsiveness.
- Correlation of retinal morphology features (e.g., area of photoreceptor loss) from AO imaging with such characteristics as visual acuity and central retinal thickness.
- Examining the relationship between peripheral nonperfusion and response to treatment.

Quality of life assessment will be important to measuring differences between the two primary treatment groups and between the secondary randomized groups (between Month 6 and Month 12), and will examine:
• Mean change from baseline in total score and subscales on vision-related quality of life as measured by the NEI VFQ-25.

Statistical methods will be used in the secondary efficacy outcomes to construct confidence limits about group differences in Month 6 to Month 12 visual acuity letter changes of good responders within primary arm after the secondary randomizations, although here we eschew non-inferiority testing in favor of obtaining point estimates and confidence limits of the group differences. The same approach of point estimates and confidence limits for Month 6 to Month 12 visual acuity letter changes will be applied in poor responders within primary arm. Because the secondary outcomes will not be stratified, these analyses are basically equivalent to 2-sample and 1-sample t-tests.

6.5. Economic Evaluation

A basic principal of economic evaluation is that of “dominance”. That is, when one treatment strategy is both less costly and more effective than another, further evaluation is unnecessary because it would be meaningless to consider the inferior strategy. The cost per dose of bevacizumab for treatment of retinal vein occlusion is much less than that of aflibercept. Therefore, one element of dominance already exists. Should it be shown that bevacizumab is more effective than aflibercept, then the conduct of an economic evaluation would be rendered unnecessary under the principal of dominance. However, SCORE2 is designed as a non-inferiority trial and thus, rather than finding that bevacizumab is superior to aflibercept, it is more likely that we will find that the two are equivalent. Should that be the case, we will determine what combination of economically significant factors (i.e., relative effectiveness and adverse events) would have to be seen in order to justify the price premium for aflibercept. Therefore, following receipt of the initial study results, we will conduct a preliminary sensitivity analysis to determine if there is such a combination of difference in effectiveness and incidence of adverse events that would be clinically viable. If that is the case, we would conduct a full economic evaluation.

A full economic evaluation will include the incidence of all adverse events (systemic and ocular) that have economic significance. These would include arterial thromboembolic events, hemorrhages, hospitalization, ocular infections, ocular edema that requires treatment, transient glaucoma, permanent blurring of vision and complications related to the injection.
All adverse events will be tracked within each study arm and considered for the model. Efficacy (i.e., visual acuity) will be used to estimate the benefit of treatment. Costs will not be collected for the clinical trial, but should a full economic evaluation be determined as necessary, costs will be calculated from a payor perspective using the Medicare allowable at the time of the evaluation.

6.6. Statistical Guidelines for Interim Monitoring by the DSMC

6.6.1. Interim Monitoring for Safety

Because rates of safety events are hard to predict, because the acceptability of an adverse event rate depends in part on effectiveness of treatment, and because an effect of treatment upon safety is expected a priori, no formal guidelines will stop the trial for safety. Instead, repeated confidence intervals based on exact binomial calculations using O’Brien-Fleming spending will apprise the DSMC of rates of specific safety variables at every DSMC meeting throughout the follow-up period.

6.6.2. Interim Monitoring for Efficacy

Upon DSMC request, we will perform interim monitoring of the primary efficacy outcome. This outcome occurs 6 months after the randomization visit. Information concerning the primary outcome accrues as participants complete their 6-month visit and thus we would consider "information time" to be the percent of the target sample that has completed this visit. Interim testing will be carried out using the Lan-DeMets\textsuperscript{32} interim monitoring boundary with an O’Brien-Fleming-type spending function. With such a parsimonious alpha spending function, the estimate of the sample size does not need to be increased for interim monitoring.

To adapt interim monitoring to non-inferiority testing, we will use the fact that, formally, rejecting the null hypothesis of bevacizumab inferiority if the upper two-tailed 95\% confidence limit for the (aflibercept-bevacizumab) difference does not exceed M is equivalent to performing a one-tailed 0.025-level hypothesis test in which the null hypothesis of the mean difference is at least M is rejected in favor its being less than M. This means that standard software for interim monitoring can easily be adapted to the non-inferiority context.
6.6.3. **Interim Monitoring for Futility**

The DSMC will consider futility as well as safety and efficacy. One method of statistically assessing futility is to use conditional power to estimate the likelihood of statistical significance given the observed efficacy results and various possible choices for the remaining results.

6.6.4. **Sample Size Re-estimation**

We plan to perform a sample size re-estimation after about half the total expected number of participants (n=162) attain their 6-month outcome, which is approximately 24 months into enrollment assuming a 36-month recruitment period. The motivation for sample size re-estimation is that the original sample size calculation was based not only on a hypothesized treatment effect, but also on hypothesized values for nuisance parameters such as variances and attrition. For SCORE2, we estimated the standard deviation of the mean change from baseline in visual acuity letter score of 16 based on information provided in the literature (CRUISE data) and data from Regeneron Pharmaceuticals Inc. in the COPERNICUS trial. We also assume 10% attrition at 6 months. If the variance or attrition estimates prove inaccurate, the sample size required for adequate power for the treatment effect may be wrong. It seems reasonable to re-estimate the nuisance parameters partway through the trial, and, based on this analysis, to re-evaluate the target sample size if necessary. To guard against a premature sample size reduction stemming from a too-low variance estimate, we will use the upper limit of the 95% confidence interval of the standard deviation as if it were the point estimate. For example, if the upper 95% confidence limit of the standard deviation observed in SCORE2 is smaller than 16, or the attrition is smaller than assumed, we could reduce the overall sample size. It would not be appropriate, however, to re-estimate the treatment effect to establish non-inferiority, as this needs to be based on assessing clinically important difference between the arms and not what is being observed in the data.

6.6.5. **Analyses and Results Requested to be Considered Prior to Recommending Early Termination**

Before recommending early termination, the DSMC will consider:

- internal consistency of primary and secondary results.
• internal consistency of primary and secondary results by subgroups defined by baseline characteristics (e.g., visual acuity categories, categories based on length of history of CRVO, and time period of enrollment).

• distribution of baseline prognostic factors among the two groups.

• consistency of primary and secondary results across clinical sites and among sites enrolling larger numbers of patients.

• possible bias in assessment of primary and secondary response variables, particularly visual acuity.

• possible impact of missing data from missed patient visits for assessment of the primary and secondary response variables.

• possible differences in concomitant interventions or medications.

• undue occurrences of unexpected SAEs or other such safety events.

7. Confidentiality and Access to Source Data / Documents

The investigators will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants in this clinical study. Medical and research records should be maintained in the strictest confidence. However, as part of the quality assurance and legal responsibilities of an investigator, the site must permit authorized representatives of the sponsor(s), the SCORE2 Coordinating Center, and regulatory agencies to examine (and when permitted or required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Unless required by the law, no copying of records with personally identifying information will be permitted. Only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information) or transmitted to the SCORE2 Coordinating Center. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals. The site will normally be notified in advance of monitoring and auditing visits.

8. Summary of Good Clinical Practice Compliance

This trial will be conducted in accordance with Good Clinical Practice (GCP) using the guidance documents and practices offered by ICH and FDA, and in accordance with the Declarations of Helsinki and the policies and procedures for the SCORE2 Coordinating Center at The Emmes
Corporation. This study will also comply with the regulations under 21 CFR Parts 50, 54, 56, and 312 under an IND application authorized by FDA.

8.1. Investigator Responsibilities (Form FDA-1572)

A Statement of Investigator (Form FDA-1572) including the names of all of the sub-investigators and selected key study personnel (e.g., pharmacist, study nurse and/or clinic coordinator, ophthalmic technician or optometric staff may be listed if desired) directly involved in the study will be completed and signed by the Principal Investigator at each site. The general responsibilities of the Investigator as acknowledged on the Form FDA-1572 are governed under the regulations in 21 CFR Parts 50, 54, 56, 312, and HIPAA. The study drug or test article may be administered only in accordance with the approved protocol and under the supervision of the Investigator or a sub-investigator listed on this form. The Investigator must maintain accurate and complete study records, including records for disposition of the test article, and an accurate and complete record of all submissions made to and received from the local Institutional Review Board (IRB) or Independent Ethics Committee (IEC), including a copy of all reports and documents submitted. Adverse experiences that are reported to the FDA as IND Safety Reports must be submitted promptly to the local IRB/IEC and the SCORE2 Coordinating Center.

Progress reports must be submitted by the Investigator to the IRB/IEC at least once per year. The IRB/IEC must be promptly notified of completion or termination of the study. Within three months of study completion or termination, a final report from the Investigator must be provided to the IRB/IEC.

The curriculum vitae (CV) or a résumé for each investigator, sub-investigator, and key study personnel must also be supplied if named on the Form FDA-1572. This form and related CVs must be supplied to the SCORE2 Coordinating Center prior to initiating the trial at each site. When necessary due to personnel changes, updated versions of the Form FDA-1572 must be forwarded to the SCORE2 Coordinating Center and copies of all versions must be maintained in study records at each site. Any CV or résumé collected at the beginning of a study should be current, and would need to be updated during the study only if substantial changes or additions are warranted (e.g., change of position or affiliation, certifications or
licensure, or significant new publications relevant to the study protocol).

8.2. Human Subjects Protection

8.2.1. Institutional Review Board or Independent Ethics Committee

Each participating institution must have an IRB or IEC constituted and operating in accordance with the regulations under 21 CFR Part 56 and authorized by the institution to review and approved materials for this trial. Because of the use of US Federal funds in this trial, all participating institutions must have a current Assurance of Compliance (either FWA or MPA) regarding their IRB/IEC on file with the DHHS Office of Human Research Protections (OHRP) before any award can be made to that institution and before participants may be enrolled in the trial. In addition, each reviewing IRB or IEC must be registered with OHRP. A list of IRB/IEC voting members, their titles or occupations, and their institutional affiliations, as well as a copy of the Assurance of Compliance, must be kept available by the institution for inspection and copying by authorized study monitors, auditors, and regulatory officials.

8.3. Data Handling and Recordkeeping

The Principal Investigator at the Participating clinical site is responsible for maintaining adherence to study procedures within the clinic. He or she must spend adequate time at the clinic observing study procedures and must hold regular discussions with staff, either one-to-one or in-group meetings, to review various aspects of the study and to solve problems that may arise. Other clinic staff members have a responsibility to report to the PI problems that could affect the quality of the data. The PI will designate one staff member to be the Clinic Coordinator for the clinic, with specific responsibility for reporting problems that have affected or can potentially affect the quality of data collected.

The Clinic Coordinator should be thoroughly familiar with clinic activities and equipment and the procedures outlined in the SCORE2 MOPP. The Clinic Coordinator should maintain an up-to-date copy of the SCORE2 MOPP close at hand and encourage all clinic personnel to consult it frequently. During Full Group Meetings the Clinic Coordinators will have the opportunity to meet with the Data Coordinating Center staff to discuss mutual problems.
8.3.1. Case Report Forms

Clinical data will be entered on electronic Case Report Forms (CRFs) in accordance with the procedures specified in the current SCORE2 MOPP and Data Management Handbook (DMH) for this trial.

8.3.2. Data Transmittal

The primary method of data transmittal to the SCORE2 Coordinating Center will be via the secure AdvantageEDC maintained by The Emmes Corporation. The current SCORE2 MOPP, DMH and access to the AdvantageEDC are available to authorized users via the SCORE2 DCC Internet web site, located at www.score2crvo.com where an assigned username and password are required for access. All data transfers between the investigational site and SCORE2 DCC via the AdvantageEDC are encrypted using SSL technologies to assure confidential data transfer.

8.4. Professional Licensure

Physicians must provide evidence of current medical licensure applicable to the study location(s) if they are practicing medicine and undertake to diagnose and/or treat participants (including administration of the test article) in this study. A physician who is a site Principal Investigator must also provide evidence of ophthalmology training before study initiation.

8.5. Human Subjects Protection Training

Documented training is required for each of the key personnel in the ethical conduct of clinical studies and in the protection of human subjects.
9. SCORE2 Long-term Follow-up (LTF) Phase

9.1. Objectives

The goals of following SCORE2 participants as part of a LTF phase of the SCORE2 protocol are to study the long-term implications of anti-VEGF treatment including visual acuity and anatomic outcomes, progression of the CRVO disease to ischemic complications, safety profile associated with the treatment, and the need for continued treatment. Since the SCORE2 LTF is intended to match a “real-world” setting, SCORE2 investigators will not be provided with study drug or re-treatment recommendations for the management of the macular edema due to the CRVO during SCORE2 LTF, thus allowing the gathering of data on types of treatment and treatment patterns that would typically be provided to CRVO patients in a clinical setting. This information will be valuable to patients and their treating ophthalmologists with respect to what they can expect in terms of number of anti-VEGF treatments and visual acuity prognosis in patients with CRVO.

Continued follow-up of SCORE2 participants at long-term visits will provide an assessment of visual, morphological, and quality of life outcomes, with the primary objectives to compare these long-term outcomes with SCORE2 baseline measurements in the overall population, and within the treatment arms originally assigned to aflibercept and bevacizumab. Comparisons between the aflibercept and bevacizumab based on original randomizations will be also made. Secondary objectives include examining outcomes within subgroups of participants based on clinical course (e.g., switching to alternate treatment and treatment schedules based on responses), as well as number and type of treatments and the investigation of the association between baseline factors and long-term visual, morphological, and quality of life outcomes.

Characterization of the safety profile of participants treated with anti-VEGF agents for macular edema due to CRVO will be done by systematically collecting important ocular and systemic events, including arterial thromboembolic events defined by the Antiplatelet Trialists’ Collaboration.
Because the LTF phase of the SCORE2 protocol is intended to gather data on types of treatment and treatment patterns that would typically be provided to CRVO patients in a clinical setting, some of the procedures and methods in place for the first year of the SCORE2 are no longer applicable. Therefore, we provide below in the following section details for following participants in the LTF phase of SCORE2.

9.2. Long-term Follow-up Methods

The SCORE2 LTF is a continuation of SCORE2, although, since this phase of the study was added after enrollment had been completed, participants will need to be re-consented. All participants known to be living and having completed the 12-month SCORE2 visit will be invited to participate in the SCORE2 LTF phase of the protocol and return to a SCORE2 clinical site for a Year 2 visit (Month 24) on or near the 2nd anniversary of their randomization month. After participant consent at the on-site visit, an ophthalmic examination will be performed, including E-ETDRS visual acuity, SD-OCT, fundus photography, ultra wide-field fluorescein angiography (at sites that performed UWFA previously), blood pressure and quality of life (QOL) assessment. Also, a review will be conducted of systemic and ocular conditions and procedures, including intravitreal injections received for the treatment of macular edema secondary to CRVO that occurred between the 12-month visit and the 24-month visit. The clinical site staff will perform medical record extraction to retrieve information on new systemic and ophthalmic conditions and procedures that occurred between the 12-month visit and the 24-month visit. These data will be added to the existing data for this participant in the SCORE2 database. Only data on consented participants will be included.

9.2.1. Eligibility Criteria

All SCORE2 participants randomized into SCORE2 who completed the Month 12 visit, and who are willing and able to provide informed consent, will be eligible to participate. Reasons for not participating in the LTF phase of SCORE2 will be documented.

9.2.2. Informed Consent

Written informed consent for the long-term follow-up phase will be obtained from participants prior to the completion of any research procedures or the collection of research data. Two identical consent forms will be signed. One original consent form is to
be kept in the participant’s study file and a second original is to be given to the
participant to take home. Participants will be made aware that ophthalmic information
obtained from visits to other ophthalmologists may be requested and that the long-term
follow-up phase does not have provisions to cover the costs of treatment.

9.2.3. Participant Visit Schedule and Assessments

Year 2 (Month 24) In-Office Visit

After consenting, the following Year 2 (Month 24) assessments will be completed (see
Table 3):

1. An interview will be conducted to obtain an update on systemic and ocular conditions
   and procedures that have occurred since the Month 12 visit. Clinic Coordinators
   should review the on-site medical record to perform medical record extraction to
   retrieve information on injections and any other therapies given to treat macular
   edema secondary to CRVO, as well as to retrieve information for systemic and ocular
   conditions and procedures performed. In addition, Clinic Coordinators may request to
   obtain medical records from other physicians and ophthalmologists to perform
   medical record extraction to retrieve information for systemic and ocular conditions
   and procedures performed at non-SCORE2 sites.

2. Blood pressure measurement.

3. Visual acuity testing and manifest refraction performed using electronic ETDRS (E-
   ETDRS). Visual acuity performed by a SCORE2 certified technician in both eyes.

4. Intraocular pressure (IOP) of both eyes (using a calibrated Goldmann applanation
   tonometer mounted on a slit-lamp or a Tonopen).

5. Ophthalmic examination of both eyes including dilated ophthalmoscopy performed
   by a SCORE2 investigator.

6. Lens assessment for cataract at the slit lamp will be performed with grading
   according to a modified Age-Related Eye Disease Study (AREDS) grading system.


8. Fundus photography and spectral domain optical coherence tomography (SD-OCT) in
   the study eye only.

9. Ultra-widefield fluorescein angiography on both eyes (in sub-set of participants in
   whom UWFA was performed at the Screening visit).
SCORE2 sites are expected to employ the same procedures and equipment used for measuring visual acuity and obtaining SD-OCT, UWFA, and fundus photographs as in the first year visits in SCORE2. NEI VFQ quality of life staffing certification and ophthalmic imaging equipment and staffing certifications obtained for SCORE2 will remain valid for the LTF phase of SCORE2. Sites performing UWFA who wish to use the Optos California software will be required to submit an image to the Reading Center for equipment re-certification. E-ETDRS visual acuity and refraction re-certification will follow the usual process. Site staff will not be masked to the initial randomization assignments. Visual acuity and OCT technicians are not required to be masked during the LTF phase.

Year 2.5 (Month 30) Telephone Assessment
Approximately six months after the Year 2 visit (Month 30), participants will be contacted by telephone by the Clinic Coordinator for an update on any systemic and ocular events that have occurred since the Month 24 visit.

Table 3: Schedule of Study Evaluations for SCORE2 LTF Phase

<table>
<thead>
<tr>
<th>Visit timing based on date of initials SCORE2 randomization:</th>
<th>Year 2 Visit (Month 24)</th>
<th>Year 2.5 Phone Call (Month 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study informed consent</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Interim systemic and ocular condition and procedure review</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>E-ETDRS Visual acuity – Both eyes</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Manifest refraction – Both eyes</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ophthalmic examination, including IOP and lens assessment – Both eyes</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NEI VFQ-25 quality of life assessment</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fundus photographs – Study eye only</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SD-OCT- Study eye only</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ultra-widefield FA (in sub-set from SCORE2 Screening) – Both eyes</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
9.2.4. Re-treatment Criteria

Any re-treatment for macular edema secondary to CRVO at the Year 2 visit or any subsequent visit is at the discretion of the investigator. Investigators will not be provided with study drug or re-treatment recommendations for the management of the macular edema due to the CRVO thus allowing the gathering of data on types of treatment and treatment patterns that would typically be provided to CRVO patients in a clinical setting. All treatments will be documented in the participant’s medical record and entered into the SCORE2 EDC.

9.3. Data and Safety Event Monitoring and Reporting

The SCORE2 Data and Safety Monitoring Committee (DSMC) will be responsible for assessing study data and study progress. The DSMC is expected to review the study approximately annually.

The SCORE2 Medical Monitor will review the safety data, present it to the DSMC for periodic review, and provide the Principal Investigator a Safety Letter when necessary.

9.3.1. Reportable Events

The systemic and ocular events listed below will be reported in the EDC by the clinical site. These events should be reported in EDC within seven days of identification by the site.

Study investigators must report safety events in accordance with regulations to their local ethics review committee (or IRB) or the central IRB, as applicable, in addition to the SCORE2 DCC.

9.3.1.1. Systemic Safety Events

- Death
- New onset hypertension and arterial thromboembolic events defined by the Antiplatelet Trialists’ Collaboration

9.3.1.2. Ocular Safety Events

- Infectious endophthalmitis –study eye only
- Noninfectious endophthalmitis –study eye only
- Retinal detachment –study eye only
New onset retinal venous occlusion – both eyes
New onset retinal arterial occlusion – both eyes
Neovascularization of the iris - study eye only
Neovascular glaucoma - study eye only
Disc or retinal neovascularization – study eye only
Nonperfusion – study eye only
Retinal tear study – eye only
Pre-retinal or vitreous hemorrhage – study eye only
Presence of silicone oil – study eye only
All ocular procedures – study eye only
Open angle glaucoma – study eye only

9.4. Statistical Analyses

9.4.1. General Statistical Approach

The LTF phase of SCORE2 will provide information on long-term outcomes for study participants initially treated in SCORE2 with one of two anti-VEGF drugs (bevacizumab and aflibercept). The primary efficacy outcome of this study is mean change in visual acuity letter score from the randomization visit in SCORE2 through Year 2 in the long-term follow-up phase of SCORE2. Secondary outcomes include SD-OCT, fundus photography, ultra-widefield fluorescein angiography and safety events. Important secondary objectives will be to evaluate:

- Patterns of treatment for macular edema due to CRVO/HRVO (number and type of treatments) and the temporal relationship with:
  - ETDRS visual acuity letter score
  - OCT features of central subfield, center point thickness, macular volume, extent of cystoid spaces and photoreceptor length (thickness of the ellipsoid zone)
  - Fundus photography features of area of retinal thickness, area of retinal hemorrhage, area of RPE atrophy
  - Ultra-widefield fluorescein angiography of peripheral retinal nonperfusion and leakage
- Estimated 2-year incidence of the ocular events based on imaging and physical reported outcomes
- Long-term incidence of death and systemic events, including new onset hypertension and arterial thromboembolic events defined by the Antiplatelet Trialists’ Collaboration

- Mean change from baseline in total score and subscales on vision-related quality of life as measured by the NEI VFQ-25

- Comparison of SCORE2 long-term outcomes with the Moorfields Eye Hospital NHS Foundation Trust-sponsored LEAVO trial (“A Multicentre Phase III Double-masked Randomised Controlled Non-Inferiority Trial comparing the clinical and cost effectiveness of intravitreal therapy with ranibizumab (Lucentis) vs aflibercept (Eylea) vs bevacizumab (Avastin) for Macular Oedema due to Central Retinal Vein Occlusion (CRVO”)’

Outcomes in this study are planned out to 2 years.

Standard statistical methodology will be applied to the analyses of the SCORE2 LTF data. For an initial examination of the data, basic descriptive statistics will be used, such as tabulations, frequency distributions, and graphical representations. This initial examination will provide a better understanding of the data, and in particular, will help to determine the appropriate approaches for data analyses. Univariate statistical techniques, parametric and non-parametric, provide statistical inferences about parameter(s) of interest, for purposes of estimation or hypothesis testing. These include t-tests and the Wilcoxon Rank Sum Test for continuous data, and Fisher’s Exact Test and the Chi-Square Test for categorical data. Regression methods can be used for statistical modeling that involve multiple predictor or repeated measurement of outcome variables. For a normally distributed outcome, these methods include analysis of variance (ANOVA) if the predictor of interest is categorical, or multiple regression analyses for continuous predictors. In the case of a binary outcome, multiple logistic regression, as described above, can be used, and for time to event data, such as time to rejection or graft failure, the Cox proportional hazards regression model can be used. Epidemiologic methods will also be used including logistic and log-linear modeling to assess possible relationships between independent and dependent variables. Generalized estimating equations (GEE) can be used under a wide variety of distribution assumptions for repeated measurement data. For long-term safety outcomes, point estimates of incidence rates will be calculated with confidence limits rather than via hypothesis testing.
9.4.2. Statistical Analysis Approach and Statistical Power in LTF Phase

The schedule of visual acuity (VA) assessments with the combination of SCORE2 and the SCORE2 LTF phase is complex (Figure 1), irregular, and partially determined by events that happen after SCORE2 randomization. In Figure 1, vertical strokes depict VA assessments, with assessments at yearly boundaries being somewhat longer strokes to help orient the viewer. SCORE2 starts at initial randomization (Month 0). For the first 6 months, there is an assessment every month. This marks the end of the SCORE2 primary outcome period. At this point, most participants are re-randomized, where some participants continue with monthly assessments (lower series of vertical strokes from Month 6 to 12), while others go on a treat and extend (TAE) schedule. In TAE, the time gap before the next visit is either 2 weeks longer than the previous gap, or 4 weeks, except that there must be a Month 12 assessment. This is symbolized in Figure 1 by the upper series of strokes from Month 6 to Month 12, which have gradually increasing gaps (but actual TAE schedules may be more irregular). Month 12 marks the last visual acuity visit in SCORE2 and the start of the SCORE2 LTF. The SCORE2 participants who are part of the LTF phase of SCORE2 do not have another visual acuity visit until their last visit, at Month 24 after randomization.

Figure 1: Pictorial depiction of combined SCORE2 (Months 0-12) and SCORE2 LTF phase (Month 24) Visual Acuity Assessments
SCORE2 baseline is time 0, while Months 1-6 occur during time period A (the SCORE2 primary outcome period), Months 7-12 occur during time period B (the SCORE2 secondary outcome period), and Month 24 (the SCORE2 LTF outcome period) occurs during time period C. The TAE schedule means that the number of observations in period B may vary from participant to participant, even if all visits are carried out per protocol.

We will analyze the SCORE2 and the SCORE2 LTF phase data jointly, using a model that is an extension of that proposed for SCORE2. More specifically:

\[
\begin{bmatrix}
Y_0 \\
Y_1 \\
\vdots \\
Y_6 \\
Y_{12} \\
Y_{24}
\end{bmatrix} = \alpha \begin{bmatrix} 1 \\
1 \\
\vdots \\
1 \\
1 \\
1
\end{bmatrix} + \begin{bmatrix}
Y_A \\
Y_A \\
\vdots \\
Y_B \\
Y_C
\end{bmatrix} + T_i \begin{bmatrix}
0 \\
0 \\
\vdots \\
\beta_A \\
\beta_B \\
\beta_C
\end{bmatrix} + \varepsilon_i
\]

Where the Y-vector contains the visual acuities of participant \(i\) at all months depicted in Figure 1 except Months 7-11, \(\alpha\) is a constant added to all terms, \([Y_A, Y_B, Y_C]\) are constants that, when added to \(\alpha\), model the mean untreated effect during periods A, B, and C\(^1\), \(T_i\) is the treatment indicator for patient \(i\), \([\beta_A, \beta_B, \beta_C]\) model the additional effect of treatment during the three time periods, and \(\varepsilon_i\) is the vector of errors for participant \(i\). Similar to SCORE2, we impose the analog of an AR(1) correlation structure on \(\varepsilon_i\). More specifically, if the time between two observations of the same participant is \(t\), we assume that the correlation between them is \(\rho^t\). The primary question of the SCORE2 LTF is whether \(\beta_C\) is significant. If so, there is a difference between the treatments applied during period A of SCORE2 that still can be seen years later, even though the eyes have departed from the M0-M6 protocol prior to the LTF phase of SCORE2.

\(^1\)Time period B is represented only by \(Y_{12}\) because the model essentially averages longitudinal measurements in a period, and the measurement schedule is correlated with outcome. For example, if bigger is better, the average of all TAE measurements in a period would be biased downward, because the TAE schedule automatically generates fewer big measurements than small measurements, since patients with low VA are told to come back more often. To avoid this, we model period B using only \(Y_{12}\), which is observed for everyone who does not drop out. Although the number of observations may also vary in period C, there is no reason to suppose that this will be correlated with outcome.
We investigated the power of this model by a simulation with 8 scenarios and 1000 iterations per scenario. The simulation used the visit schedule and model described above, and made the following other assumptions:

- 360 patients enroll in SCORE2
- Based on data from SCORE2, monthly attrition is about 0.5%. We also assumed an additional 4% loss between Month 12 and Month 24 from some SCORE2 patients declining participation in the SCORE2 LTF. This means about a 10% loss between Month 12 and Month 24.
- Based on Month 0 to Month 12 data from SCORE2, the correlation between 2 values from the same patient, one month apart, is about 0.89.
- Standard deviation of measurements = 16
- $\alpha = \gamma_A = \gamma_B = \gamma_C = 0$
- $\beta_A = \beta_C = \beta_C = \beta$, with values of $\beta$ given in Table 5 below. That is, there is a constant treatment effect during the three periods.

Table 4 shows the predicted proportion of participants remaining in the SCORE2 to SCORE2 LTF as a function of time. The combined studies will experience about a 15% loss from enrollment into SCORE2 to the end of the SCORE2 LTF at 2 years.

Table 4: Predicted attrition in SCORE2 and the SCORE2 LTF phase as a function of time

<table>
<thead>
<tr>
<th>Month</th>
<th>Fraction remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>2</td>
<td>0.99</td>
</tr>
<tr>
<td>3</td>
<td>0.99</td>
</tr>
<tr>
<td>4</td>
<td>0.98</td>
</tr>
<tr>
<td>5</td>
<td>0.98</td>
</tr>
<tr>
<td>6</td>
<td>0.97</td>
</tr>
<tr>
<td>12</td>
<td>0.94</td>
</tr>
<tr>
<td>24</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Table 5 shows 2-tailed 0.05-level simulated power for the three separate tests of treatment effect as a function of the assumption about the value of $\beta$, the size of the treatment effect in the three periods. The first row of Table 5 demonstrates that the type I
error of the three tests is as desired. The second row of Table 5 show that power for period C is 78% at 24 months if the treatment effect is about an E-ETDRS visual acuity letter score of 5.

Table 5: Simulated Two-tailed 0.05-level power for the three tests of treatment effect as a function of $\beta$. (Each row based on 10,000 iterations)

<table>
<thead>
<tr>
<th>Period</th>
<th>$\beta$ (E-ETDRS visual acuity letter score)</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>1</td>
<td>0.90</td>
<td>0.78</td>
</tr>
</tbody>
</table>

9.4.3. Approach to Missing Data

The SCORE2 LTF phase will likely have more dropouts than SCORE2 because some SCORE2 participants, and perhaps some SCORE2 sites, will not agree to participate in the SCORE2 LTF phase. Both these phenomena would be sources of missing data. One may be tempted to discount refusal to participate by deliberately limiting the generalizability of SCORE2 LTF phase (that is, letting the results in the SCORE2 LTF phase apply only to those who agree to participate in the SCORE2 LTF phase), but this would make it difficult to know how to apply follow-up results to a future population. The approach to addressing missing data in the analysis within the SCORE2 LTF phase is addressed below.

Data governed by a missingness process that is independent of the data values, both observed and unobserved, are called data Missing Completely at Random (MCAR). Ignoring the fact of missingness is appropriate for MCAR data, and will yield an unbiased estimate of the population mean in a MCAR sample. But often such a simple missingness process is not realistic. Data in which missing values depend only on observed values are called Missing at Random (MAR). The question of whether missing data are MAR or MCAR depends on what auxiliary covariates are available. As more auxiliary variables are added to the data, the constellations of their covariate values become more numerous and smaller, and the claim that the missing data are MCAR
within those constellations (thus MAR) becomes intuitively more appealing. It also seems reasonable to regard data missing from sites that refuse to participate in the LTF phase as being MAR. Multiple Imputation (MI) is a technique that allows efficient implementation with MAR data. In MI, missing individual data values are repeatedly imputed with the observed data being kept constant, the resulting simulated treatment effect averaged over the repeats, and a method provided whereby the variance of the resulting point estimate is correctly estimated (providing the MAR assumption is correct). Moreover, the technique is not limited to just taking averages, but may be used with virtually any of the parameter estimation methods now popular in modern statistics to produce MAR estimates of parameters. But MCAR and MAR are just assumptions. Perhaps very small observations tend to be missing, even within the constellations of observed covariates. This would mean that neither the MCAR nor the MAR estimates are unbiased. When the missingness process still depends on the values of the missing variables, even after the observed data values have been taken into consideration, we say the data are Missing Not At Random (MNAR). In the SCORE2 LTF phase, data may become MNAR because participants with low vision become discouraged and drop out, or because participants with good vision become convinced that they no longer need their treatment/follow-up regimen, and strike out on their own, or that the cost of treatment is prohibitive. Since missing data are, in fact, missing, there is no way to tell what type of missingness process is actually operating. In the absence of a way to tell what values the missing observations have, the SCORE2 LTF phase analysis approach will be to perform a sensitivity analysis, which reveals the extent to which different assumptions about missingness affect the MAR conclusions of the trial. The recent introduction of the MNAR command to SAS MI implementation provides a rigorous framework in which pattern-mixture sensitivity analysis may be easily carried out.

9.5. Confidentiality and Access to Source Data / Documents

The investigators will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants in this clinical study. Medical and research records should be maintained in the strictest confidence. However, as part of the quality assurance and legal responsibilities of an investigator, the site must permit authorized representatives of the sponsor(s), the SCORE2 Coordinating Center, and regulatory agencies
to examine (and when permitted or required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Unless required by the law, no copying of records with personally identifying information will be permitted. Only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information) or transmitted to the Data Coordinating Center. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals. The site will normally be notified in advance of monitoring and auditing visits.

9.6. Summary of Good Clinical Practice Compliance

The LTF phase of SCORE2 will be conducted in accordance with Good Clinical Practice (GCP) using the guidance documents and practices offered by ICH and FDA, and in accordance with the Declarations of Helsinki and the policies and procedures for the SCORE2 Data Coordinating Center at The Emmes Corporation. Each institution must maintain their IRB or IEC approval and not enroll any participants in the LTF phase of the protocol until that IRB or IEC has reviewed and approved materials for this trial. Because of the use of US Federal funds in this trial, all participating institutions must have a current Assurance of Compliance (either FWA or MPA) regarding their IRB/IEC on file with the DHHS Office of Human Research Protections (OHRP). In addition, each reviewing IRB or IEC must be registered with OHRP. A list of IRB/IEC voting members, their titles or occupations, and their institutional affiliations, as well as a copy of the Assurance of Compliance, must be kept available by the institution for inspection and copying by authorized study monitors, auditors, and regulatory officials.

9.7. Data Handling and Recordkeeping

The Principal Investigator (PI) at the participating clinical site is responsible for maintaining adherence to study procedures within the clinic. He or she must spend adequate time at the clinic observing study procedures and must hold regular discussions with staff, either one-to-one or in-group meetings, to review various aspects of the study and to solve problems that may arise. Other clinic staff members have a responsibility to report to the PI problems that could affect the quality of the data. The PI will designate at least one staff member to be the Clinic Coordinator, with specific responsibility for reporting problems that
have affected or can potentially affect the quality of data collected. The Clinic Coordinator should be thoroughly familiar with clinic activities and equipment and the procedures needed to participate in the LTF phase of SCORE2.

9.7.1. Case Report Forms
Clinical data will be entered on electronic Case Report Forms (CRFs) in accordance with the procedures specified in SCORE2 LTF policy and procedure manuals.

9.7.2. Data Transmittal
The primary method of data transmittal to the SCORE2 Data Coordinating Center will be via the secure AdvantageEDC maintained by The Emmes Corporation. All data transfers between the investigational site and the DCC via the AdvantageEDC are encrypted using SSL technologies to assure confidential data transfer.

9.8. Professional Licensure
Physician investigators must provide evidence of current medical licensure applicable to the study location(s) if they are practicing medicine and undertake to diagnose and/or treat participants in this study. Physician investigators must also provide evidence of board-certification in ophthalmology and completion of a retinal fellowship.

9.9. Good Clinical Practice and Human Subjects Protection Training
Documented training is required for each of the key personnel in good clinical practice (i.e., Principal Investigators and clinical coordinators) and in the protection of human subjects (i.e., all research personnel who interact with study participants).
10. References


### Appendix 1: Schedule of Study Evaluations

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Screening/ Baseline*</th>
<th>Months 1 to 5 Q1 Month</th>
<th>M6</th>
<th>Months 7 to 11 Q1 Month</th>
<th>M12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine pregnancy test</td>
<td>X²</td>
<td>X³</td>
<td>X³</td>
<td>X³</td>
<td></td>
</tr>
<tr>
<td>Medical/ocular history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual acuity</td>
<td>X²,5</td>
<td>X⁵</td>
<td>X⁵</td>
<td>X⁵</td>
<td>X³</td>
</tr>
<tr>
<td>Manifest refraction</td>
<td>X⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOP</td>
<td>X⁴,5</td>
<td>X⁵</td>
<td>X⁵</td>
<td>X⁵</td>
<td>X³</td>
</tr>
<tr>
<td>Ophthalmic examination⁷</td>
<td>X⁴,5</td>
<td>X⁵</td>
<td>X⁵</td>
<td>X⁵</td>
<td>X³</td>
</tr>
<tr>
<td>NEI VFQ-25 quality of life assessment</td>
<td>X⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lens assessment⁸</td>
<td>X⁴,6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fundus photographs</td>
<td>M3F²,6</td>
<td>M3F⁶</td>
<td>M3F⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD-OCT</td>
<td>X²,6</td>
<td>X⁶</td>
<td>X⁶</td>
<td>X⁶</td>
<td></td>
</tr>
<tr>
<td>Ultra-widefield FA⁹</td>
<td>X⁴,5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adaptive optics⁹</td>
<td></td>
<td>X⁵,14</td>
<td>X⁵</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Genetic Biorepository**
- Genetic biorepository informed consent¹³: X
- Saliva specimen collection¹³: X

**SCORE2 Treatments**
- Anti-VEGF injection: Month 1 – 5: X
- Anti-VEGF injection: Months 6 -11 in Good Responders: X¹⁰
- Dexamethasone injection: Months 6 and PRN at Month 9, 10 or Month 11 in Poor or Marginal Responders: X¹¹
- Aflibercept injection: Months 6, 7, 8 and TAE in Poor or Marginal Responders: X¹²

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*Note: The baseline visit can occur on the same day as the screening visit but must be completed within 21 days of the screening visit.*

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M= month, Q1=every month, M3F= Modified 3-Field photos, FA= Fluorescein Angiogram, TAE= Treat and Extend

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1696

1697

1698

1699

1700
1 Only in women of child-bearing potential.
2 To be performed within 8 days prior to randomization.
3 Prior to each study injection.
4 To be performed within 21 days prior to randomization.
5 Examination data to be collected on both eyes.
6 Examination data to be collected on study eye only.
7 Examination includes both a dilated fundus examination and a slit-lamp examination.
8 To be performed using the modified AREDS lens grading system.
9 Ultra-widefield FA and adaptive optics will be performed at the subgroup of sites that have this ability.
10 Axial length measurement may also be requested.
11 Retreatment in eyes with good response should be administered between Months 6 and 11 according to the randomized assignment of q4 weeks or TAE.
12 Treatment with dexamethasone should be administered at Months 6 and PRN at Month 9, 10 or 11 for eyes with poor or marginal response among those initially randomized to aflibercept.
13 Treatment with aflibercept should be administered at Months 6, 7, 8 and TAE eyes with poor or marginal response among those initially randomized to bevacizumab.
14 Salvia specimens may be obtained at the Baseline visit following randomization, and can be collected either before or after the first injection. If the specimen is not obtained at the baseline visit, the specimen may be collected at a follow-up visit. Consent must be obtained prior to specimen collection.
15 Adaptive optics to be performed between randomization and the Month 1 visit.
Appendix 2: Aflibercept Package Insert
Supplied separately.
Appendix 3: Bevacizumab Clinical Investigator’s Brochure

Supplied separately.
Appendix 4: Dexamethasone Package Insert

Supplied separately.
EYLEA® (aflibercept) Injection
For Intravitreal Injection

Initial U.S. Approval: 2011

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:
- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME) in Patients with DME
- Diabetic Retinopathy (DR) in Patients with DME

2 DOSAGE AND ADMINISTRATION

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months).
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

3 DOSAGE FORMS AND STRENGTHS

- 40 mg/mL solution for intravitreal injection in a single-use vial

4 CONTRAINDICATIONS

- Ocular or periocular infection
- Active intraocular inflammation
- Hypersensitivity

5 WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection.
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

6 ADVERSE REACTIONS

- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, and vitreous detachment.

7 PATIENT COUNSELING INFORMATION

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Nursing Mothers
- Pediatric Use
- Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Central Retinal Vein Occlusion (CRVO)
- Macular Edema Following Branch Retinal Vein Occlusion (BRVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR) in Patients with DME

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

Revised: 5/2016

See 17 for PATIENT COUNSELING INFORMATION.
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
1.3 Diabetic Macular Edema (DME)
1.4 Diabetic Retinopathy (DR) in Patients with DME

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

For ophthalmic intravitreal injection, EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [see Clinical Studies (14.1)]. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly) [see Clinical Studies (14.2), (14.3)].

2.4 Diabetic Macular Edema (DME)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [see Clinical Studies (14.4)]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR) in Patients with DME

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [see Clinical Studies (14.5)]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration

EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x 1½-inch injection needle.

**Vial**

The glass vial is for single use only.

1. Remove the protective plastic cap from the vial (see Figure 1).

**Figure 1:**

2. Clean the top of the vial with an alcohol wipe (see Figure 2).

**Figure 2:**

3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle from its pouch and remove the 1-mL syringe supplied in the carton from its pouch. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 3).

**Figure 3:**

4. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.

5. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figures 4a and 4b).

**Figure 4a:**

6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

7. Remove the filter needle from the syringe and properly dispose of the filter needle. **Note:** Filter needle is **not** to be used for intravitreal injection.

8. Remove the 30-gauge x 1½-inch injection needle from the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).

**Figure 5:**

9. When ready to administer EYLEA, remove the plastic needle shield from the needle.

10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).

**Figure 6:**

11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe (see Figures 7a and 7b).

**Figure 7a:**

**Figure 7b:**

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Appendix II: Aflibercept Package Insert
2.7 Injection Procedure
The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad-spectrum microbicide should be given prior to the injection. Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay [see Patient Counseling Information (17)]. Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS
Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [see Adverse Reactions (6.1)]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [see Dosage and Administration (2.7) and Patient Counseling Information (17)].

5.2 Increase in Intraocular Pressure
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [see Adverse Reactions (6.1)]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [see Dosage and Administration (2.7)].

5.3 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in the Warnings and Precautions (5) section of the labeling:
- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD)
The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months [see Clinical Studies (14.1)].

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>EYLEA (N=1824)</th>
<th>Active Control (ranibizumab) (N=595)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hemorrhage</td>
<td>25%</td>
<td>28%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Cataract</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Corneal epithelium defect</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Detachment of the retinal pigment epithelium</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Retinal pigment epithelium tear</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO)
The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT) [see Clinical Studies (14.2), (14.3)].

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>CRVO (N=218)</th>
<th>BRVO (N=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EYLEA (N=218)</td>
<td>Control (N=142)</td>
<td>EYLEA (N=91)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Corneal epithelium defect</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Cataract</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.
Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Baseline to Week 52</th>
<th>Baseline to Week 100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA (N=578)</td>
<td>Control (N=287)</td>
</tr>
<tr>
<td></td>
<td>EYLEA (N=578)</td>
<td>Control (N=287)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>28%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>17%</td>
<td>31%</td>
</tr>
<tr>
<td>Eye pain</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>11%</td>
</tr>
<tr>
<td>Cataract</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>9%</td>
<td>19%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Corneal epithelium defect</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastrochisis, cleft palate, ectodactyly, intestinal atresia, spina bifida, encephalomalacencephal, heart and major vessel defects, and skeletal malformations (fused vertebrae, ribs, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Females of reproductive potential should use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

8.3 Nursing Mothers
It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Vascular endothelial growth-factor-A (VEGF-A) and placental growth factor (PLGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PLGF binds only to VEGFR-1, which is also present on the surface of leukocytes. Activation of these receptors by VEG-F can result in neovascularization and vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PLGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

12.2 Pharmacodynamics
Neovascular (Wet) Age-Related Macular Degeneration (AMD)
In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions [see Clinical Studies (14.1)].

Macular Edema Following Retinal Vein Occlusion (RVO)
Reductions in mean retinal thickness were observed in COPERNICUS, GALILEO, and VIBRANT at week 24 compared to baseline. Anatomic data were not used to influence treatment decisions [see Clinical Studies (14.2), (14.3)].

Diabetic Macular Edema (DME)
Reductions in mean retinal thickness were observed in VIVID and VISTA at weeks 52 and 100 compared to baseline. Anatomic data were not used to influence EYLEA treatment decisions [see Clinical Studies (14.4)].

12.3 Pharmacokinetics
EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD, RVO, or DME, following intravitreal administration of EYLEA, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept-VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept-VEGF complex).

Absorption/Distribution
Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD, RVO, and DME, the mean Cmax of free aflibercept in the plasma was 0.02 mcg/mL (range: 0.005 to 0.045 mcg/mL), 0.05 mcg/mL (range: 0.005 to 0.081 mcg/mL), and 0.03 mcg/mL (range: 0 to 0.076 mcg/mL), respectively and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as 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.

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

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

Specific Populations

Renal Impairment
Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. Similar results were seen in patients in a RVO study and in patients in a DME study. No dose adjustment based on renal impairment status is needed for either wet AMD, RVO, or DME patients.

Other
No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).
13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in mice with intravenous administration of aflibercept at weekly doses ranging from 3 to 30 mg per kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Intravenous administration of the lowest dose of aflibercept assessed in mice (3 mg per kg) resulted in systemic exposure (AUC) that was approximately 1500 times higher than the systemic exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible within 20 weeks after cessation of treatment.

13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg. Similar effects were not seen in clinical studies. Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg per eye. At the NOAEL of 0.5 mg per eye in monkeys, the systemic exposure (AUC) was 56 times higher than the exposure observed in humans after an intravitreal dose of 2 mg. Similar effects were not seen in clinical studies [see Clinical Studies (14)].

14 CLINICAL STUDIES

14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were randomized and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW1 and VIEW2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5Q4). Patient ages ranged from 49 to 99 years with a mean of 76 years. In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Data are available through week 52. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5Q4 group.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 4 and Figure 8 below.

**Table 4: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies**

<table>
<thead>
<tr>
<th></th>
<th>VIEW1</th>
<th>VIEW2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA 2 mg Q8 weeks</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td></td>
<td>EYLEA 2 mg Q4 weeks</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td>Full Analysis Set</td>
<td>N=301</td>
<td>N=304</td>
</tr>
<tr>
<td>N=306</td>
<td>N=309</td>
<td>N=291</td>
</tr>
</tbody>
</table>

**Efficacy Outcomes**

<table>
<thead>
<tr>
<th>Proportion of patients who maintained visual acuity (%) (&lt;15 letters of BCVA loss)</th>
<th>Difference (%) (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>94% 95% 94% 95% 95% 95%</td>
<td>(-3.2, 4.4) (-2.4, 5.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean change in BCVA as measured by ETDRS letter score from Baseline</th>
<th>Difference (%) (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.9 10.9 8.1 8.9 7.6 9.4</td>
<td>(-2.9, 4.0) (-4.0, 3.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference (%) (95.1% CI)</th>
<th>NS-LOCF (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6 1.3 0.6 0.3 0.3 0.3</td>
<td>-0.3 0.6 0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference (%) (95.1% CI)</th>
<th>NS-LOCF (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 0.5 0.3 0.9 0.9 0.9</td>
<td>-1.1 0.9 -1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference (%) (95.1% CI)</th>
<th>NS-LOCF (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.4 -7.7 7.0 6.6 6.6</td>
<td>-10.2 4.9 -12.19</td>
</tr>
</tbody>
</table>

**14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)**

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with EYLEA) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4), or sham injections (control group) administered every 4 weeks for a total of 6 injections. Patient ages ranged from 22 to 89 years with a mean of 64 years. In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 5 and Figure 9 below.

**Table 5: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies**

<table>
<thead>
<tr>
<th></th>
<th>COPERNICUS</th>
<th>GALILEO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td></td>
<td>N=73</td>
<td>N=114</td>
</tr>
</tbody>
</table>

**Efficacy Outcomes**

<table>
<thead>
<tr>
<th>Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)</th>
<th>Difference (%) (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12% 56% 22% 60%</td>
<td>(12.9, 56.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weighted Difference (%) (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38.3% (24.4, 52.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)</th>
<th>Difference in LS mean (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4.0 (18.0)</td>
<td>21.7% (17.3, 26.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference in LS mean (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.7% (10.7, 18.7)</td>
</tr>
</tbody>
</table>

* Difference is EYLEA 2 mg Q4 weeks minus Control
* Difference and CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline factors; 95.1% confidence intervals were presented to adjust for the multiple assessments conducted during the study.
* p<0.01 compared with Control
* LS mean and CI based on an ANCOVA model

**Figure 8: Mean Change in Visual Acuity from Baseline to Week 52 in VIEW1 and VIEW2 Studies**

**Figure 9: Mean Change in Visual Acuity from Baseline to Week 52 in COPERNICUS and GALILEO Studies**
Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity, retinal perfusion status, and CRVO duration) in each study and in the combined analysis were in general consistent with the results in the overall populations.

14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)
The safety and efficacy of EYLEA were assessed in a 24-week, randomized, multi-center, double-masked, controlled study in patients with macular edema following BRVO. A total of 181 patients were treated and evaluable for efficacy (91 with EYLEA) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4) or laser photocoagulation administered at baseline and subsequently as needed (control group). Patient ages ranged from 42 to 94 years with a mean of 65 years.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. At week 24, the EYLEA 2 mg 04 group was superior to the control group for the primary endpoint.

Detailed results from the analysis of the VIBRANT study are shown in Table 6 and Figure 10 below.

Table 6: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in VIBRANT Study

<table>
<thead>
<tr>
<th>VIBRANT</th>
<th>EYLEA 2 mg Q4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>N=90</td>
</tr>
<tr>
<td>EYLEA</td>
<td>N=91</td>
</tr>
</tbody>
</table>

**Efficacy Outcomes**

- Proportion of patients who gained at least 15 letters in BCVA from Baseline (%):
  - Control: 26.7%
  - EYLEA: 52.7%

- Weighted Difference \(^a\) (%) (95% CI):
  - Control: 26.6% (13.0, 40.1)

- Mean change in BCVA as measured by ETDRS letter score from Baseline (SD):
  - Control: 17.0 (11.9)
  - EYLEA: 6.9 (12.9)

- Difference in LS mean \(^b\) (95% CI):
  - Control: 10.5 (7.1, 14.0)

\(^a\) Difference is EYLEA 2 mg Q4 weeks minus Control
\(^b\) Difference and CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (≥ 20/200 and ≤ 20/200)
\(^c\) p<0.01 compared with Control
\(^d\) LS mean and CI based on an ANCOVA model

14.4 Diabetic Macular Edema (DME)
The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Patient ages ranged from 23 to 87 years with a mean of 63 years.

Of those, 576 were randomized to EYLEA groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 5 initial monthly injections (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the EYLEA groups could receive laser and patients in the laser group could receive EYLEA.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. Efficacy of both EYLEA 2Q8 and EYLEA 2Q4 groups was statistically superior to the control group. This statistically superior improvement in BCVA was maintained at week 100 in both studies.
Results from the analysis of the VIVID and VISTA studies are shown in Table 7 and Figure 11 below.

**Table 7: Efficacy Outcomes at Weeks 52 and 100 (Full Analysis Set with LOCF) in VIVID and VISTA Studies**

<table>
<thead>
<tr>
<th></th>
<th>VIVID</th>
<th>VISTA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA 2 mg Q8 weeks</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td>Full Analysis Set N=135</td>
<td>N=136</td>
<td>N=132</td>
</tr>
</tbody>
</table>

**Efficacy Outcomes at Week 52**

| Mean change in BCVA as measured by ETDRS letter score from Baseline (SD) | 10.7 (9.3) | 10.5 (9.6) | 1.2 (10.6) | 10.7 (8.2) | 12.5 (9.5) | 0.2 (12.5) |
| Difference in LS mean (97.5% CI) | 9.1* (6.3, 11.8) | 9.3* (6.5, 12.0) | 10.5* (7.7, 13.2) | 12.2* (9.4, 15.0) |
| Proportion of patients who gained at least 15 letters in BCVA from Baseline (%) | 33.3% | 32.4% | 9.1% | 31.1% | 41.6% | 7.8% |
| Adjusted Difference (%) (97.5% CI) | 24.2% (13.5, 34.9) | 23.3% (12.6, 33.9) | 23.3% (13.5, 33.1) | 34.2% (24.1, 44.4) |

**Efficacy Outcomes at Week 100**

| Mean change in BCVA as measured by ETDRS letter score from Baseline (SD) | 9.4 (10.5) | 11.4 (11.2) | 0.7 (11.8) | 11.1 (10.7) | 11.5 (13.8) | 0.9 (13.9) |
| Difference in LS mean (97.5% CI) | 8.2* (5.2, 11.3) | 10.7* (7.6, 13.8) | 10.1* (7.0, 13.3) | 10.6* (7.1, 14.2) |
| Proportion of patients who gained at least 15 letters in BCVA from Baseline (%) | 31.1% | 38.2% | 12.1% | 33.1% | 38.3% | 13.0% |
| Adjusted Difference (%) (97.5% CI) | 19% (8.0, 29.3) | 26.1% (14.8, 37.5) | 20.1% (9.6, 30.6) | 25.8% (15.1, 36.6) |

* After treatment initiation with 5 monthly injections
* LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, protocol specified stratification factors were included in the model.
* Difference is EYLEA group minus Control group
* p<0.01 compared with Control
* Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors.

**Figure 11: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 100 in VIVID and VISTA Studies**

Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study were in general consistent with the results in the overall populations.

14.5 Diabetic Retinopathy (DR) in Patients with DME

In the VIVID and VISTA studies, an efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The ETDRS-DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies [see Clinical Studies (14.4)].

All enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. At week 100, the proportion of patients improving by at least 2 steps on the ETDRS-DRSS was significantly greater in both EYLEA treatment groups (2Q4 and 2Q8) when compared to the control group.
Results from the analysis of ETDRS-DRSS at week 100 in the VIVID and VISTA studies are shown in Table 8 below.

Table 8: Proportion of Patients who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Week 100 (LOCF a) in VIVID and VISTA Studies

<table>
<thead>
<tr>
<th></th>
<th>VIVID</th>
<th>VISTA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA 2 mg Q8 weeks b</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td>Evaluable Patients c</td>
<td>N=101</td>
<td>N=97</td>
</tr>
<tr>
<td>Number of patients with a ≥2-step improvement on ETDRS-DRSS from Baseline (%)</td>
<td>32 (32%)</td>
<td>27 (28%)</td>
</tr>
<tr>
<td>Difference e (%) (97.5% CI)</td>
<td>24%f (12, 36)</td>
<td>21%f (9, 33)</td>
</tr>
</tbody>
</table>

a Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable)
b After treatment initiation with 5 monthly injections
c The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline
d Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors
e Difference is EYLEA minus Control group
f p<0.01 compared with Control

Results of the evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity) on the proportion of patients who achieved a ≥2-step improvement on the ETDRS-DRSS from baseline to week 100 were, in general, consistent with those in the overall population.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each Vial is for single eye use only. EYLEA is supplied in the following presentation [see Dosage and Administration (2.6) and (2.7)].

<table>
<thead>
<tr>
<th>NDC NUMBER</th>
<th>CARTON TYPE</th>
<th>CARTON CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>61755-005-02</td>
<td>Vial</td>
<td>one single-use, sterile, 3-mL, glass vial designed to deliver 0.05 mL of 40 mg/mL EYLEA one 19-gauge x ½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert</td>
</tr>
</tbody>
</table>

STORAGE
EYLEA should be refrigerated at 2°C to 8°C (36°F to 46°F). Do Not Freeze. Do not use beyond the date stamped on the carton and container label. Protect from light. Store in the original carton until time of use.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [see Warnings and Precautions (5.1)].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [see Adverse Reactions (6)]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.
Appendix III: Bevacizumab Investigator’s Brochure

SCORE2 Investigator’s Brochure
Bevacizumab for Intravitreal Injection

Version 3.0 — 06 Jul 2015
CONFIDENTIAL

Prepared for Clinical Investigators
in conjunction with the protocol entitled

Study of COMparative Treatments for REtinal Vein Occlusion 2
[SCORE2]

A study funded under grants 1U10EY023521-01, 1U10EY023529-01, and 1U10EY023533-01 from the
National Eye Institute at the National Institutes of Health

Investigator’s Brochure prepared by the SCORE2 Data Coordinating Center at
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Document Version Approvals:

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Michael Ip, MD 07/09/2015
Michael S. Ip, MD, Study Co-Chair
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2.0 CHANGE SUMMARY FROM PRIOR EDITION

Safety information was added to Section 7.3 and 7.4 to indicate that, based on studies in pregnant rabbits and the drug’s mechanism of action, systemic administration of bevacizumab may cause harm to an embryo or fetus. Even though the intravitreal dose of bevacizumab is about 700 times lower than systemic doses per unit body weight, women of reproductive potential should be advised of the potential risk to an embryo or fetus. Women of reproductive potential should be advised to use effective contraception during treatment with, and for 6 months after the last dose of, bevacizumab.
3.0 SUMMARY

This SCORE2 Investigator’s Brochure for bevacizumab (Avastin®) focuses on the background of anti-vascular endothelial growth factor (anti-VEGF) therapy and descriptions of the known risks and potential benefits of intraocular anti-VEGF therapy for macular edema secondary to retinal vein occlusion (RVO), and in particular the use of bevacizumab when administered by intravitreal injection. SCORE2 is a randomized non-inferiority study designed to compare two anti-VEGF agents, aflibercept (Eylea®) and bevacizumab, used to treat macular edema secondary to central retinal vein occlusion (CRVO). Aflibercept received FDA marketing approval to treat macular edema secondary to RVO, and more recently to treat diabetic macular edema (DME). Bevacizumab has FDA marketing approval for certain non-ocular cancers, but is currently used off-label to treat macular edema. Both of these anti-VEGF products are routinely reimbursed by third party payors when treating macular edema secondary to CRVO, but the treatment costs vary, and to establish the non-inferiority of bevacizumab would have important economic and public health implications.

Although intravitreal corticosteroid therapy is a readily available treatment option for macular edema secondary to RVO in general and CRVO in particular, initial treatment with anti-VEGF therapy is now used most commonly. This is due to the perception that anti-VEGF treatments are more efficacious and safer than corticosteroid therapy. Corticosteroid therapy is typically used as a rescue therapy for eyes that have an unsuccessful result with initial anti-VEGF therapy, and corticosteroids are used this way in SCORE2 as well. There are other anti-VEGF options available to treat macular edema related to CRVO or other ocular conditions. These include the two anti-VEGF agents that gained the earliest FDA marketing approvals for intravitreal use (though indications varied), which were pegaptanib sodium (Macugen®) and ranibizumab (Lucentis®). Bevacizumab is currently supplied (unlike the other products approved specifically for ocular use) in larger vials needed for the systemic dosing for which it has marketing approval. So in practice, commercially available bevacizumab is usually aliquoted and transferred into smaller vials or a suitable syringe for more economic, off-label intraocular use.

Intravitreal injection of bevacizumab is widely used in off-label treatments, with estimates now ranging up to several hundred thousand injections per year in the US, based on survey information from pharmacies that prepare individual doses for such injections.

To investigate non-inferiority between aflibercept and bevacizumab, the primary outcome in SCORE2 is based on visual acuity, with secondary outcomes based on retinal thickness, area of retinal ischemia, rates of neovascular complications, and cost-effectiveness analyses. The SCORE2 protocol provides details on the trial rationale, design, enrollment qualifications, assessments and outcome measures. SCORE2 investigators need to follow the approved protocol carefully for the study to obtain valid and useful results.

4.0 INTRODUCTION

Macular edema is a major cause of vision loss in patients with RVO. RVO is the most common retinal vascular disorder after diabetic retinopathy. RVO is estimated to affect 1-2% of the population older than 40 years and 16 million persons worldwide. Macular edema is the most frequent cause of vision loss in patients with RVO. Extensive studies have established that VEGF plays a central role in the development of several pathologies characterized by neovascularization and increased vascular permeability leading to macular edema. These include the ocular conditions of proliferative diabetic retinopathy, neovascular glaucoma, age-related macular degeneration (AMD), and RVO.
all these conditions, VEGF contributes to increased permeability across both the blood-retinal and blood-brain barriers. Retinal ischemia and local anoxia causes increased VEGF production, which in turn causes vascular leakage and macular edema. A logical therapeutic approach for these conditions is to target and block the increased VEGF activity linked to macular edema. Bevacizumab was originally developed for systemic anti-tumor activity. During a time when the related ocular drug, ranibizumab, was unavailable and the need was strong for a local rather than systemic anti-VEGF therapy, Philip Rosenfeld pioneered studies in 2004-2005 that led to the rapid adoption of bevacizumab as an alternate anti-VEGF compound for intraocular use.

The results of the Central Vein Occlusion Study (CVOS, 1988-1994) showed that macular laser photocoagulation did not change the natural course of untreated macular edema associated with CRVO. However, recent advances have shown that pharmacotherapy with corticosteroids and molecules that inhibit the action of VEGF (i.e., anti-VEGF) have a beneficial effect on the natural course of this disease. Currently, there are two corticosteroids (triamcinolone and the dexamethasone implant) and three anti-VEGF drugs (bevacizumab, ranibizumab and aflibercept) that are widely available to treat macular edema secondary to CRVO. Each drug, individually, has been compared (most with level 1 evidence) with observation or a placebo and has been shown to have a robust effect on the disease. However, these drugs have not been compared directly against each other in well-controlled trials and there has not been guidance regarding which drug(s) may be used secondarily, as a rescue treatment, in cases where initial therapy is not successful. There is uncertainty in the retina community as to which treatment to use initially and at what frequency. SCORE2 will assess whether one of the most commonly used anti-VEGF drugs, bevacizumab, is non-inferior to a second generation anti-VEGF drug, aflibercept, for the treatment of macular edema secondary to CRVO. Rescue therapy with corticosteroids, in cases where initial therapy is not successful, will also be evaluated.

SCORE2 is a multicenter, prospective, randomized, phase III clinical trial in which all participants enrolled will be followed for 12 months. As a non-inferiority trial, SCORE2 will have study eyes randomized 1:1 to intravitreal bevacizumab (1.25 mg) every 4 weeks vs. intravitreal aflibercept (2.0 mg) every 4 weeks. SCORE2 aims to determine if bevacizumab is non-inferior to aflibercept for the treatment of macular edema associated with CRVO, with the primary outcome of visual acuity measured at 6 months.

Bevacizumab and ranibizumab are closely related in molecular structure and in mechanism of action and may be thought of as first-generation anti-VEGF drugs. These two drugs have also been demonstrated in a number of clinical trials for AMD to have clinical equivalence. Aflibercept may be deemed a second generation anti-VEGF drug with a different molecular structure and with a broader mechanism of action (in addition to antagonism of VEGF-A, there is antagonism of VEGF-B and placental derived growth factor). As a result of the related molecular structure of bevacizumab and ranibizumab, and the similar clinical effects of these two drugs in AMD, as well as a lack of a cost differential between ranibizumab and aflibercept, SCORE2 will directly compare bevacizumab with aflibercept. SCORE2 will assess whether bevacizumab is non-inferior to aflibercept (with the ability to test for superiority) for the treatment of decreased vision associated with macular edema secondary to CRVO.


5.0 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

Bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA, CAS Registry Number: 216974-75-3) is a recombinant humanized monoclonal IgG1 antibody (MAb) consisting of 93% human and 7% murine sequences. Bevacizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in both in vitro and in vivo assay systems. To cause its anti-VEGF activity, bevacizumab binds to VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of vascular endothelial cells. The interaction of native VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. In the early developmental studies with bevacizumab, administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

The commercially-available bevacizumab product is not currently labeled for intravitreal injection. But bevacizumab is, in conjunction with other anti-cancer agents, indicated for metastatic colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma, and metastatic renal cell carcinoma. Bevacizumab for these cancer indications is normally diluted in 0.9% Sodium Chloride Injection, USP, and administered by intravenous (IV) infusion at doses ranging from 5 to 15 mg/kg every 2-3 weeks.

Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab has an approximate molecular weight of 149 kD and is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Bevacizumab includes 1,320 amino acids containing human constant region sequences and murine light and heavy chain Complementarity Determining Region (CDR) sequences. The human framework contributes to 93% of the overall protein sequence.

Bevacizumab is a full-length IgG1κ isotype antibody composed of two identical light chains (214 amino acid residues) and two heavy chains (453 residues). The heavy chains demonstrate C-terminal heterogeneity (lysine variants) and also contain one N-linked glycosylation site at asparagine 303. The oligosaccharides are of complex biantennary structures with a core fucose and with the two branches terminating mainly with zero (G0), one (G1) or two (G2) galactose residues. The G0 glycoform predominates at approximately 80% relative abundance. Each light chain is covalently coupled through a disulfide bond at cysteine 214 to a heavy chain at cysteine 226. The two heavy chains are covalently coupled to each other through two inter-chain disulfide bonds, which is consistent with the structure of a human IgG1.

The primary sequence of the bevacizumab light chain is as follows:

```
DIQMTQSPSLSLAVGSGLVPRITCQASQDISNYLWQQMQPQGAPKVIYFTSSLHSVPS
RFSGSGSDFTTLTISSLQPEFDASYCQYSCPSTYPFSTFGSGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTSASVCLNNFYPREAKVQQKDNLQSGNSQESVTEEDSKSTYSLSTLT
LSKADYEHKDYACEVTHQGLSSPVTNSRGE
```

The primary sequence of the bevacizumab heavy chain is as follows:

```
EVQLVESGGGLVPGGLSLRLSACSGTFTNGMNNVRQPAPGKLEWVGWINTYCTQFHY
ADEFKRRFTTSLEDTSKSTAYLGMSLRAEDTAVYCAKPHYGYSSHWYFDVWQGTLVT
```
A computerized rendering of the 3-dimensional structure of bevacizumab appears as follows (light chains are darker, heavy chains are lighter):¹¹

**Commercial Preparation**

Bevacizumab (Avastin®) is supplied by the original manufacturer in preservative-free, single use vials (either 100 mg or 400 mg per vial, both at 25 mg/mL). It is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for IV infusion. Original, unopened Avastin vials are stable for up to 24 months when stored at 2-8° C (36-46° F) and protected from light. Vials should not be frozen or shaken.

The 100 mg original packaged product contains 4 mL of Avastin [NDC 50242-0060-01] and is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP.

The 400 mg product contains 16 mL of Avastin [NDC 50242-0061-01] and is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP.
5.1 Packaging Bevacizumab for SCORE2

a) Commercially available bevacizumab (Avastin®) is re-packaged for SCORE2 using sterile technique without dilution or addition of preservatives into either: smaller, sterile single-dose glass vials (approximately 0.18 mL, 25 mg/mL), or

b) sterile, pre-filled tuberculin (TB) syringes (to deliver up to 0.1 mL, 25 mg/mL).

Either type of re-packaged bevacizumab as provided by the sponsor (i.e., the smaller vials or the pre-filled syringes) may be used in SCORE2.

For SCORE2 study participants, re-packaged bevacizumab is labeled for investigational use in accordance with 21 CFR 312.6(a). Use of non-study containers of bevacizumab obtained from other sources during the trial (e.g., routine commercial supplies) is not allowed in SCORE2 study participants.

Re-packaged bevacizumab labeled and shipped to investigators for SCORE2 use must remain in a controlled inventory held under proper refrigerated conditions (2°-8° C) and should not be used for any other purpose, including transfers into general clinical practice or a non-clinical laboratory setting.

Regardless of the re-packaging type (small vials or pre-filled syringes), re-packaged bevacizumab for SCORE2 must be used by the date indicated on the package. Beyond the date shown on the re-packaged SCORE2 study product, bevacizumab at study sites must be quarantined, accounted for and subsequently destroyed or returned in accordance with study procedures for study product disposition.

For bevacizumab that is provided in pre-filled syringes, long-term storage of re-packaged bevacizumab for SCORE2 is not possible at this time because inadequate data is available to extend the use period beyond 90 days from the re-packaging date.12 If this dating period is revised during the study, all active investigators will be notified if they have received pre-filled syringes.

5.2 Bevacizumab Administration for SCORE2

Bevacizumab for SCORE2 is administered by intravitreal injection, 1.25 mg (0.05 mL) per treatment, using a small bore (e.g., 30 ga) sterile needle. Sites using the smaller vials must draw-up the bevacizumab from the vials into a suitable syringe using aseptic technique, preferably in the treatment or operating room shortly before use, and switch to a fresh needle for the intravitreal injection. Detailed recommendations for the bevacizumab injection technique are given in the SCORE2 Manual of Policies and Procedures (MOPP). The sponsor may provide the bevacizumab re-packaged in vials for SCORE2 in boxed kits with suitable needles and an empty sterile syringe.

5.3 Name and Address of Manufacturers/suppliers for SCORE2 Bevacizumab Study Supplies

The preservative-free, single use bevacizumab (Avastin®) vials [NDC 50242-0060-01 and NDC 50242-0061-01] are manufactured by Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990.

The contents of the commercially-available Avastin® vials are aliquoted and re-packaged using sterile techniques into smaller, single-dose containers or syringes suitable for SCORE2 study use.
Quality assurance sterility testing is conducted on each batch of re-packaged bevacizumab product for SCORE2.

The re-packing of bevacizumab into smaller, sterile vials for SCORE2 is performed at the University of Pennsylvania Investigational Drug Service (IDS) pharmacy, 3400 Civic Center Boulevard, Building 421, 10th Floor, Room 122, Philadelphia, PA 19104-5158.

If used, re-packaging of bevacizumab into sterile, 1.0 mL TB syringes for SCORE2 may be performed at Leiter’s Compounding, 17 Great Oaks Blvd., San Jose, CA 95119.

The methodology for aliquoting bevacizumab and the sterility assurance procedures used when re-packing bevacizumab in TB syringes follows closely the method described by the Bascom Palmer Eye Institute at the University of Miami for sterile product transfers into TB syringes.13 Qualified alternate sources of re-packaged bevacizumab may also be used in the study, if approved by the SCORE2 Executive Committee.

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6.0 NONCLINICAL STUDIES

Nonclinical studies have been conducted by the manufacturer primarily in preparation for systemic dosing of bevacizumab in cancer indications, and included studies in vitro and in vivo models with mice, rats, rabbits and cynomolgus monkeys. Unless otherwise noted in this section, the following nonclinical details regarding systemic dosing are taken primarily from the 2005 EMEA document, “Avastin, INN-bevacizumab: scientific discussion.”14 Detailed references are found in the EMEA document, which is available on-line, but the original references are omitted here. VEGF is described first, as this is the target of the anti-VEGF bevacizumab.

6.1 Nonclinical Pharmacology

**Biological Activity of VEGF**

VEGF is a major regulator of angiogenesis during normal and pathological processes, including that associated with tumor growth. VEGF has a key regulatory function during developmental angiogenesis. A well-documented in vitro activity of VEGF is the ability to promote growth of vascular endothelial cells (EC) derived from arteries, veins and lymphatics, as well as certain non-endothelial cells. VEGF was shown to be a survival factor for ECs, both in vitro and in vivo. VEGF stimulated production of surfactant proteins by cultured type 2 pneumocytes. VEGF induces vasodilatation in vitro, and is thought to play a role in inflammation due to its ability to induce vascular leakage. VEGF displays chemotactic effects on endothelial cells and increases expression of proteolytic enzymes in endothelial cells involved in stromal degradation. VEGF has also effects on bone marrow-derived cells, promoting monocyte activation and chemotaxis. VEGF enhanced colony formation by mature subsets of granulocyte-macrophage and erythroid progenitor cells that had been stimulated with a colony stimulating factor. VEGF also displays immune effects via inhibition of maturation of antigen presenting dendritic cells.

Native VEGF is a basic, heparin-binding, homodimeric glycoprotein of 45,000 Daltons. These properties correspond to those of VEGF165, the predominant VEGF isoform. The human VEGF gene has been located to chromosome 6p21.3 and is organized in eight exons separated by seven introns. Alternative splicing was shown to result in four major VEGF isoforms (VEGF121, VEGF165, VEGF189, and VEGF206) consisting of 121, 165, 189, and 206 amino acids following signal sequence cleavage, respectively. Less frequent splice variants also have been reported, including VEGF145, VEGF183, and VEGF165b. An additional level of regulation of VEGF biological activity is provided by the proteolytic cleavage mechanism, including all VEGF isoforms, resulting in the VEGF110 form.

VEGF binds two related receptor tyrosine kinases (RTK), named Flt-1 (VEGFR-1), KDR/Flik-1 (VEGFR-2). The Fms-like-tyrosine kinase Flt-4 (VEGFR-3) is a member of the same family of RTKs but is not a receptor for VEGF, binding instead to VEGFC and VEGFD8. In addition to these RTKs, VEGF interacts with a family of coreceptors, the neuropilins. Binding of VEGF to VEGFR-1 and VEGFR-2 induces the homodimerization of two receptor subunits, which in turn triggers autophosphorylation of their tyrosine kinase domains located within the cytoplasm. Autophosphorylation of the tyrosine kinase domains subsequently engages a series of specific signal transduction events, ultimately regulating the various biological activities of VEGF on endothelial cells. Most of VEGF’s mitogenic and survival activity appears to be mediated by VEGFR-2, including the expression of the anti-apoptotic proteins Bcl-2 and A1. Survival
signaling by VEGFR-2 is mediated by the PI3 kinase/Akt pathway. VEGFR-2 was also shown to
induce other signal transduction pathways including phospholipase C gamma and mitogen-
activated kinases MAPK p44/42.

**Biological Activity of Bevacizumab**

Bevacizumab selectively binds with high affinity to all isoforms of human VEGF and neutralizes
VEGF’s biologic activity through a steric blocking of the binding of VEGF to its receptors Flt-1
(VEGFR-1) and KDR (VEGFR-2) on the surface of endothelial cells. Receptor activation
normally induces their tyrosine phosphorylation and the subsequent series of signal transduction
events that elicit mitogenic and pro-survival activity signals for the vascular endothelial cells.
Since there is a very low or undetectable expression of VEGF receptors in most normal tissues
(with exception of renal glomeruli) but a significant up-regulation in the vasculature of many
tumors (including colorectal cancer), the neutralization of VEGF by bevacizumab provides the
rationale a relative specific inhibition of the tumor angiogenesis and thereby inhibition of tumor
growth and metastasizing.

The pharmacological activities of bevacizumab were evaluated in a number of *in vitro* assays
using recombinant human VEGF. Bevacizumab and A4.6.1 (the closely-related murine parental
homolog with strong anti-VEGF activity) were compared for their ability to inhibit bovine
capillary endothelial cell proliferation in response to VEGF. The two monoclonal antibodies were
essentially equivalent, both in potency and efficacy. The ED50s were, respectively, 50 ± 5 and 48
± 8 ng/mL. A level of 90 % inhibition was achieved at 500 ng/mL for both antibodies.
Bevacizumab and A4.6.1 are pharmacologically equivalent when tested with human cells, human
tissues or human VEGF isoforms. The murine homolog A4.6.a was used in many early
pharmacological studies due to its equivalence to the humanized bevacizumab and its high
affinity to human VEGF isotypes.

**6.2 Systemic Pharmacokinetics and Product Metabolism in Animals**

In xenograft models of cancer in nude mice, bevacizumab or A4.6.1 administration resulted in
marked growth inhibition of a variety of tumor types, including rhabdomyosarcoma,
glioblastoma, leiomyosarcoma, ovarian carcinoma, prostate carcinoma, colon adenocarcinoma,
Wilms’ tumor, hepatoblastoma, neuroblastoma, breast carcinoma, melanoma, and pancreatic
cancer. Dose-dependent tumor growth inhibition was observed independent of tumor location and
route of administration (IV, IP, and intra-tumoral). Growth inhibition of primary tumors was
obtained with early as well as with late treatment initiation. The effects as assessed by tumor size
and/or weight ranged from 25% to >95% inhibition relative to control treatment. Immunohistochemistry of tumors revealed moderate to complete inhibition of tumor angiogenesis. Magnetic Resonance Imaging studies showed that A4.6.1 is able to counteract the
permeability-enhancing effects of VEGF.

In three different animal models inoculated with human tumor cells (colon carcinoma, prostate
and Wilms’ tumor), treatment with A4.6.1 markedly inhibited primary tumor growth and reduced
metastasis dissemination to liver and lung.
**Pharmacokinetics**

Pharmacokinetic (PK) studies following single dose administration were performed in mouse, rat, rabbit, and cynomolgus monkey. Examination of pharmacokinetic parameters following multiple doses was primarily conducted in repeat-dose toxicity studies in rabbit and cynomolgus monkey. Pharmacokinetics were in most studies evaluated following IV administration, which was the intended clinical administration route.

Concentrations of bevacizumab in serum from rabbit, rat, cynomolgus monkey, and mouse, as well as rabbit amniotic fluid were measured by enzyme-linked immunosorbent assay (ELISA). The same principle was used for measurement of antibodies to bevacizumab in rabbit serum, cynomolgus monkey serum and amniotic fluid from rabbit.

**Absorption-Bioavailability**

Absorption of bevacizumab subsequent to a single intraperitoneal (IP) or subcutaneous (SC) administration has been examined in mouse, rat, and cynomolgus monkey. Absorption subsequent to IP administration was complete in mouse. SC administration resulted in a slower absorption that was complete in mouse (>100%) and cynomolgus monkey (98%), but with a bioavailability of 69% in rat.

Following IV administration of bevacizumab to mice, rats, rabbits, and cynomolgus monkeys, bevacizumab concentrations decreased with an initial half-life \( t_{1/2a} \) of approximately 1 day followed by a slower phase, with a terminal half-life \( t_{1/2b} \) that was between approximately 1 and 2 weeks. Nonlinear PK parameters were observed in mice, rats, and rabbits following administration of doses of < 1 mg/kg.

Bevacizumab clearance (CL) was slower following administration of higher doses. In mice, the CL was approximately two times faster at a dose of 0.8 mg/kg, compared to the CL estimated after administration of 8.5 mg/kg. In rats, CL was 1.7 times faster at a dose of 0.664 mg/kg compared to 10.1 mg/kg. In rabbit CL after a single dose of 0.5 mg/kg was approximately twice as fast as after four repeated doses of 10 mg/kg bevacizumab. This difference was reflected in increased half-time.

In cynomolgus monkeys, following single IV administration, bevacizumab PK was linear over the range of 2-50 mg/kg. The mean CL was approximately 6 mL/kg/day, and the \( t_{1/2a} \) and \( t_{1/2b} \) were ≤ 1 and 10 days, respectively.

PK parameters, estimated following multiple-dose systemic administration of bevacizumab in the 4-, 13-, and 26-week toxicology studies in cynomolgus monkeys, were also generally consistent with those estimated following single-dose administration. Although evidence of non-linear kinetic was also observed in cynomolgus monkey receiving 50 mg/kg weekly for 26 weeks, these findings were likely to be due to methodological aspects and inter-individual variation, and it was possible to conclude that kinetic was linear in cynomolgus monkey. Thus, no alteration in disposition was observed upon administration of multiple systemic doses.

**Secondary Pharmacodynamics**

No dedicated studies of safety pharmacology were performed. Nonclinical studies of up to 26 weeks duration were performed with bevacizumab in cynomolgus monkeys and rabbits. Drug-related effects were consistent with the inhibition of VEGF-dependent angiogenesis. These
studies revealed dose related effects on sites of active neo-angiogenesis and include an increase in hypertrophied chondrocytes, subchondral bony plate formation, and inhibition of vascular invasion of the growth plate in young adult cynomolgus monkeys. Decreased ovarian and uterine weights and absence of corpora lutea were observed in female cynomolgus monkeys after treatment with bevacizumab. Both the physeal and ovarian changes were reversible with cessation of treatment.

**Distribution, Metabolism, and Excretion**

Two and 48 hours after IV bolus administration of $^{125}$I-bevacizumab in rabbits, trichloracetic acid (TCA)-precipitable radioactivity was localized primarily in plasma (approximately 10-fold higher than in tissues). Radioactivity decreased by nearly 2.5-fold between 2 and 48 hours for both $^{125}$I-bevacizumab, and the isotype control. The organs that exhibited the highest levels of radioactivity per gram of tissue were, in decreasing order, kidney > testis > spleen > heart > lung > thymus (ranging from 0.069-0.018% TCA-precipitable dose/g of tissue). Tissue distribution profiles of $^{125}$I-bevacizumab and $^{125}$I-rhuMAb E25 were similar.

Bevacizumab was shown to distribute into fetal serum and into the amniotic fluid in two reproduction toxicity studies conducted in rabbit.

In the distribution study in rabbit, minimal degradation was noted for as long as 48 hours for both $^{125}$I-bevacizumab and the control monoclonal IgG, $^{125}$I-rhuMAb E25. The degradation pattern appeared to vary from tissue to tissue. At 48 hours, intact $^{125}$I-bevacizumab remained the predominant band in most tissues analyzed, with similar results for the labeled control antibody, rhuMAb E25. The metabolism of bevacizumab was similar to that of the control MAb.

No specific study has been conducted to evaluate excretion. In the pharmacokinetic study in rabbit, less than 10% of the radioactivity in the urine at 2 and 48 hours post dose was TCA-precipitable.

**6.3 Systemic Animal Toxicology**

The toxicology program was designed primarily to support IV administration of bevacizumab for the original anti-cancer indications. These toxicology studies were performed in cynomolgus monkeys and rabbits. Bevacizumab was administered alone for up to 26 weeks or in combination with commonly used chemotherapy regimens in cynomolgus monkeys. Cynomolgus monkey VEGF is predicted to have a protein sequence identical to that of human VEGF. Bevacizumab also binds rabbit VEGF, although with a lower affinity than for human VEGF; the dissociation constant ($K_d$) is 8.0 nM for rabbit VEGF compared with 1.1 nM for human VEGF. Due to the lower affinity of bevacizumab to rabbit VEGF compared to human VEGF, the design of toxicology studies in rabbits used higher doses, and was of shorter duration to avoid the development of anti-drug antibodies.

No single-dose toxicity studies were performed.

No genotoxicity, mutagenecity or carcinogenicity studies were performed.

No local tolerance study was performed.

No studies have been conducted to investigate excretion in milk of lactating animals.

No specific studies in animals have been conducted to evaluate the effect on fertility.
Twice weekly IV administration of bevacizumab for 4 or 13 weeks were carried out in young adult to adult cynomolgus monkeys. Additionally, a 26-week IV with a 12-week recovery was conducted in adult cynomolgus monkeys.

In the 4-week study, young monkeys were treated with bevacizumab vehicle or bevacizumab 2, 10 or 50 mg/kg twice weekly. There were no overt clinical signs of toxicity, and no treatment-related effects were noted on body weight, food consumption, blood pressure, rectal body temperature, respiration rates, ECG, ophthalmic or electroretinographic observations or clinical pathology (including clinical chemistry, urinalysis). Enlarged spleens were reported for one male and one female in the 50 mg/kg group. One male given 50 mg/kg had slight, multifocal renal hemorrhage. There were no pathologic changes to explain the finding. In the male 10 and 50 mg/kg group, microscopic findings of physeal dysplasia of the distal femur were noted. The physeal dysplasia was slight to moderate at 10 mg/kg and moderate to severe at 50 mg/kg. This was characterized by thickening of the growth plate, clusters of hyperplastic chondrocytes, and a distinct zone of cessation of bone growth. Physeal dysplasia was present in both males following 4 week recovery, being slight in 1 animal and severe in the other. Minimal diffuse degeneration and necrosis of the metaphyseal bone marrow was present in the recovery animal with severe physeal dysplasia. Antibodies to bevacizumab were not detected in any animal at any time point.

The 13 week study used similar dose levels and regimen as the 4 week study. No toxicity on body weight, blood pressure, ECG, ophthalmology or clinical pathology parameters was observed. One 50 mg/kg male had notably decreased serum protein and albumin and increased cholesterol at week 13, coinciding with the histopathologic finding of glomerulonephritis in this animal. The finding was considered idiopathic and unrelated to treatment. Ovarian and uterine weights were reduced in females at 10 or 50 mg/kg. The changes coincided with a reduced number or absence of corpora lutea. Distinct corpora lutea were essentially absent in females at 50 mg/kg and were noted in only two of four females at 10 mg/kg. Following 4 week’s recovery, females at 50 mg/kg had an absence of corpora lutea, but ovarian and uterine weight were no longer decreased, suggesting that the effect on female reproductive function is at least partially reversible upon treatment cessation. A dose-dependent increased incidence and severity of physeal dysplasia (as described for the 4-week study) was noted, and in males it was seen at all dose levels and regarded as moderately severe at 10 and 50 mg/kg. Additionally, linear fissuring of the cartilaginous growth plate was occasionally observed. In females, physeal dysplasia was minimal to slight at 10 or 50 mg/kg. Physeal dysplasia was present but less severe after 4 week’s recovery, suggesting repair of damaged growth plate cartilage. The bias toward males was not considered a direct gender effect, since most of the treated females had closed growth plates at treatment initiation. Antibodies to bevacizumab were not detected in any animal at any time point.

In the 26-week study, adult monkeys (4 to 7 years old) were treated once weekly at 2, 10 or 50 mg/kg or twice weekly at 10 mg/kg. Treatment induced no effects on physical examination, ECG, blood pressures, radiograms, ophthalmology, hematology or urinalysis. At 10 mg/kg (twice weekly) and 50 mg/kg, mildly lower albumin and albumin-to-globulin ratio and moderately higher globulin were seen in males. Additionally, body weights, weight gain and food consumption were reduced for males in these groups. The body weight effects were no longer evident following 12-week’s recovery. Serum from one control animal at study day 15 and serum from one 50 mg/kg animal at day 183 were positive for antibodies to bevacizumab. The responses were very weak (just above the minimal detectable level) and were directed to the Fab portion of
bevacizumab. A positive result in the control animal was considered to be due to assay interference, and all other time points for this animal were negative.

Given the physeal dysplasia observed in studies of bevacizumab in cynomolgus monkeys following 4 to 26 weeks of treatment, an investigative study in rabbits was conducted to assess the suitability of the rabbit for further study of physeal dysplasia. In contrast to the effect noted in monkeys, bevacizumab did not inhibit vascular invasion or induce subchondral bony plate formation in rabbits at doses up to 75 mg/kg. However, the duration of dosing in rabbits is limited by development of antibodies to bevacizumab; this short exposure period may possibly be insufficient for physeal dysplasia to develop.

**Reproductive and Developmental Studies**

Studies on embryo-fetal development were performed in rabbit. Bevacizumab administration (10-100 mg/kg) induced a decrease in maternal body weight and body weight gain throughout the gestation period and a decrease in food consumption during the post-dose period in high-dose animals (GDs 12, 15 and 18). Food consumption was reduced in the same animals. Average fetal body weights were reduced in the same dose group. Antibodies to bevacizumab were detected in fetal serum of 37% (11/30) of the treated does and in the amniotic fluid of 20% (6/30) of the treated does. Bevacizumab was detected in maternal serum, fetal serum and amniotic fluid of most rabbits at GD 29 (11 or 17 days after the last dose). In most cases, fetal serum concentrations were greater than maternal serum concentrations with a median ratio of fetal serum:maternal serum concentrations of 1.87. Amniotic fluid concentrations were generally lower than maternal serum concentrations with a median ratio of 0.197.

In another study in rabbit, a dose-related significant decrease in maternal body weight gain and significant mean body weight loss were observed in the two higher dose groups (30 and 100 mg/kg on GDs 6, 9, 12, 15 and 18). Fetal body weights were significantly reduced in all treatment groups. The number of late resorptions was increased in the 100 mg/kg dose group, resulting in an increase in the total number of resorptions and the per cent dead or resorbed fetuses per litter. There was a dose-related increase in fetal malformations, and in the two higher dose groups the number of litters with malformations was statistically significantly increased as compared to the control group. The fetal NOAEL was less than 10 mg/kg, since all treatment doses reduced fetal weights and number of ossification sites, whereas the two higher treatment doses produced a statistically significant increase in multiple malformations.

A treatment-related delay in wound healing was observed in rabbits at doses of 0.5 mg/kg, which was below the proposed human clinical IV dose.

In reproductive toxicity studies, female cynomolgus monkeys treated with 0.4 to 20 times the recommended human systemic dose of bevacizumab exhibited arrested follicular development or absent corpora lutea as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.
Pregnant rabbits dosed with 1 to 12 times the human systemic dose of bevacizumab every three days during the period of organogenesis (gestation day 6-18) exhibited teratogenic effects, decreases in maternal and fetal body weights, and increased number of fetal resorptions. Teratogenic effects included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; meningocele; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges. There are no data available regarding the level of bevacizumab exposure in the offspring.

6.4 Ocular Studies in Rabbits

Toxicology and Ocular Pharmacokinetics

An experimental study was performed to investigate the potential intraocular toxicity associated with intravitreal bevacizumab injection. Ten rabbits were injected intravitreally with 1.25mg (0.05 mL) bevacizumab; fellow eyes served as control eyes and received intravitreal injections of 0.05 mL saline. ERG measurements were performed at 3 hours, 3 days, 1 week, 2 weeks, and 4 weeks post-injection. VEP measurements were performed at 4 weeks post-injection. Histological examination of treated and control retina were performed at 4 weeks post-injection. No evidence of intraocular toxicity was observed in this small study with 4 weeks of follow-up. 15

In another study, the vitreous half-life of 1.25 mg intravitreally-administered bevacizumab was observed to be 4.32 days in the rabbit eye. Concentrations of >10 μg/mL of bevacizumab were maintained in the vitreous for 30 days post injection, and bevacizumab concentrations in the aqueous humor of the injected eye were highest 3 days after injection and peaked at 37.7 μg/mL. In the same study, maximal serum concentrations of 3.3 μg/mL bevacizumab were observed 8 days later, with concentrations falling to below 1 μg/mL by 29 days after injection. Concentrations of bevacizumab in the aqueous humor of the fellow eye were remained low and peaked at 29.4 ng/mL 1 week after injection. The bevacizumab concentration in the vitreous of the fellow eye ranged from 0.35 ng/mL at 1 day to 11.17 ng/mL at 4 weeks. 16

Another study, also performed in rabbits, estimated the vitreous half-life of 1.25 mg bevacizumab delivered intravitreally to be 6.61 days. 17

The pharmacokinetics of bevacizumab after topical, subconjunctival and intravitreal administration has also been compared in rabbits. There was substantial penetration of the bevacizumab to the retina/choroid layers after a single subconjunctival injection of 1.25 mg bevacizumab (mean maximum concentration 295.8 ng/g) and after a single intravitreal injection of 1.25 mg (93,990 ng/g), but only very low concentrations (< 20 ng/g) were observed after 7 repeated topical administrations. Following intravitreal injection of 1.25 mg bevacizumab in the rabbit eyes, maximal concentrations in plasma (2087 ng/g) and fellow eye retina/choroid (224.2 ng/g) were still considered to be at levels effective for anti-VEGF activity. 18

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7.0 EFFECTS IN HUMANS

Bevacizumab has been extensively studied in humans as a systemic chemotherapeutic agent in conjunction with other agents for cancer treatment, and received its initial FDA approval for the treatment of metastatic colorectal cancer. Subsequently bevacizumab been approved for the treatment of non-squamous- non-small cell lung cancer, glioblastoma, and metastatic renal cell carcinoma. Human data (off-label use) have also demonstrated efficacy of bevacizumab for treatment of choroidal neovascularization associated with age-related macular degeneration and macular edema associated with several ocular conditions, including retinopathy due to retinal vein occlusion. Intravitreally administered bevacizumab also appears effective in improving visual acuity results in patients with diabetic macular edema. Although systemically administered bevacizumab is associated with adverse events including poor wound healing, hemorrhage, venous and arterial thromboembolic events and hypertension (see Section 6.3), intravitreally administered bevacizumab does not appear to be associated with large increases in these types of events.

7.1 Systemic Pharmacokinetics and Metabolism in Humans

The following is taken from the bevacizumab FDA package insert:

The pharmacokinetic profile of bevacizumab administered intravenously was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of bevacizumab weekly, every 2 weeks, or every 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (range 11-50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of bevacizumab every 2 weeks was 2.8. The clearance of bevacizumab varied by body weight, gender, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger Vc (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens below the median. In Study 1, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with bevacizumab as compared to females and patients with low tumor burden. The relationship between bevacizumab exposure and clinical outcomes has not been explored.

7.2 Intravitreally Administered Pharmacokinetics and Metabolism in Humans

The pharmacokinetics of intravitreally administered bevacizumab was assessed in 30 eyes of 30 patients which had not previously undergone vitrectomy. A single injection of 1.5 mg bevacizumab was performed at baseline and an aqueous humor sample was then obtained during cataract surgery performed between 1 and 53 days after injection. The elimination half-time was calculated to be 9.82 days, with a peak concentration 1 day after injection. The mean concentration was 33.3 μg/mL.

7.3 Safety and Efficacy in Humans – Systemic Administration

The following is taken from the bevacizumab package insert (references omitted), where patients received repeated IV bevacizumab treatments in conjunction with other anti-cancer agents:
The data below reflect exposure to bevacizumab in 2661 patients with metastatic colorectal cancer (mCRC), non-squamous non-small cell lung cancer (NSCLC), metastatic breast cancer (MBC), glioblastoma, or metastatic renal cell carcinoma (mRCC) in controlled (Studies 1, 2, 4, 5, 6 and 9) or uncontrolled, single arm (Study 7) trials treated at the recommended dose and schedule for a median of 8 to 16 doses of bevacizumab. The population was aged 21-88 years (median 59), 46.0% male and 84.1% white. The population included 1089 first- and second-line mCRC patients who received a median of 11 doses of bevacizumab, 480 first-line metastatic NSCLC patients who received a median of 8 doses of bevacizumab, 592 MBC patients who had not received chemotherapy for metastatic disease received a median of 8 doses of bevacizumab, 163 glioblastoma patients who received a median of 9 doses of bevacizumab, and 337 mRCC patients who received a median of 16 doses of bevacizumab.

**Surgery and Wound Healing Complications with Systemic Administration**

Bevacizumab impairs wound healing in animal models. In clinical trials, administration of bevacizumab was not allowed until at least 28 days after surgery. The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving bevacizumab as compared to patients receiving only chemotherapy. Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus bevacizumab as compared to 4% (1/25) of patients who received bolus-IFL alone. In Study 7, events of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma: 3/84 patients in the bevacizumab alone arm and 1/79 patients in the bevacizumab plus irinotecan arm.

**Hemorrhage with Systemic Administration**

Bevacizumab can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving bevacizumab compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving bevacizumab ranged from 1.2 to 4.6%.

The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus bevacizumab compared with patients receiving bolus-IFL plus placebo. All but one of these events were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic events were more frequent in patients receiving bolus-IFL plus bevacizumab when compared to those receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%).

Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving bevacizumab and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone. In clinical studies in non–small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of bevacizumab were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 bevacizumab-treated patients (rate 1.2%, 95% CI 0.06%-5.93%).
Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two patients had Grade 3–4 hemorrhage.

**Venous Thromboembolic Events with Systemic Administration**

The incidence of Grade 3-4 venous thromboembolic events was higher in patients with mCRC or NSCLC receiving bevacizumab with chemotherapy as compared to those receiving chemotherapy alone. The risk of developing a second subsequent thromboembolic event in mCRC patients receiving bevacizumab and chemotherapy was increased compared to patients receiving chemotherapy alone. In Study 1, 53 patients (14%) on the bolus-IFL plus bevacizumab arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event. Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus bevacizumab and 3% (1/30) of patients receiving bolus-IFL alone.

The overall incidence of Grade 3-4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus bevacizumab and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the incidence of the following Grade 3–4 venous thromboembolic events was higher in patients receiving bolus-IFL plus bevacizumab as compared to patients receiving bolus-IFL plus placebo: deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

**Hypertension with Systemic Administration**

The incidence of severe hypertension is increased in patients receiving bevacizumab as compared to controls. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

**Proteinuria with Systemic Administration**

The incidence and severity of proteinuria is increased in patients receiving bevacizumab as compared to controls. Nephrotic syndrome occurred in 1% of patients receiving bevacizumab in clinical trials, in some instances with fatal outcome. In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy. The safety of continued bevacizumab treatment in patients with moderate to severe proteinuria has not been evaluated. Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 9. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 9, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of bevacizumab. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of bevacizumab in 30% of the patients who developed proteinuria (Study 9).

**Congestive Heart Failure with Systemic Administration**

The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving bevacizumab compared to 0.6% in the control arm across indications. In patients with MBC, the incidence of Grade 3-4 congestive heart failure (CHF) was increased in patients in the bevacizumab plus paclitaxel arm (2.2%) as compared to the control arm (0.3%). Among patients
receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for patients receiving bevacizumab as compared to 0.6% for patients receiving paclitaxel alone. The safety of continuation or resumption of bevacizumab in patients with cardiac dysfunction has not been studied.

**Gastrointestinal Perforation with Systemic Administration**

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in bevacizumab treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 2.4% across clinical studies. The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of bevacizumab.

**Arterial Thromboembolic Events with Systemic Administration**

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving bevacizumab compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the bevacizumab containing arms was 2.4% compared to 0.7% in the control arms. Among patients receiving bevacizumab in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years. The safety of resumption of bevacizumab therapy after resolution of an ATE has not been studied.

**Embryo-fetal Toxicity with Systemic Administration**

Based on animal studies and the drug’s mechanism of action, systemic administration of bevacizumab may cause harm to an embryo or fetus. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with, and for 6 months after the last dose of, bevacizumab.

Limited postmarketing reports describe cases of fetal malformations with use of systemic bevacizumab in pregnancy; however, these reports are insufficient to determine drug associated risks.

**7.4 Safety and Efficacy in Humans – Ocular Administration**

**Early Studies and Case Reports**

The observation that fluorescein-conjugated bevacizumab leaked from laser-induced choroidal neovascularization after systemic administration to a cynomolgus monkey led to the initiation of an open-label prospective clinical study, the Systemic bevacizumab for Neovascular AMD (SANA) Study. Data on the first 9 patients enrolled in this study through the first 12 weeks of follow-up have been published. Patients were treated with a baseline infusion of bevacizumab (5mg/kg), followed by one or two additional doses given at 2-week intervals. In the study eyes,
significant improvements in visual acuity were observed within 1 week of treatment, and by 12 weeks, the median and mean visual acuity letter scores increased by 8 letters (p=0.011) and 12 letters (p=0.008), respectively. The median and mean central retinal thickness (CRT) measurements decreased by 157 μm (p=0.008) and 177 μm (p=0.001), respectively. In the fellow eyes at 12 weeks, median and mean visual acuity improvement was 27 letters (p=0.018) and 16 letters (p=0.012), respectively, and the median and mean CRT decreased by 59 μm (p=0.028) and 92 μm (p=0.06). Fluorescein angiography demonstrated a marked reduction or an absence of leakage of choroidal neovascularization in all study eyes. No serious ocular or systemic adverse events were observed. By 6 weeks, the only adverse event observed was a mild elevation of systolic blood pressure, controlled by changing or initiating antihypertensive medication; by 12 weeks, the elevation of systolic blood pressure was no longer significant.

Case reports of the intravitreal use of bevacizumab have also been published. In one case, a 63-year-old woman with predominantly classic subfoveal choroidal neovascularization associated with age-related macular degeneration in her left eye, progressing despite treatment with photodynamic therapy/intravitreal triamcinolone acetonide and pegaptanib, was administered a single 1.0mg intravitreal injection of bevacizumab (0.04 mL of commercially available bevacizumab at a concentration of 25 mg/mL). Visual acuity prior to injection was 20/125. One week following injection, the patient reported resolution of visual distortion and optical coherence tomography (OCT) demonstrated resolution of subretinal fluid. At 4 weeks, visual acuity remained stable and the subretinal fluid had not recurred. In the other case, a 68-year-old man with macular edema associated with central retinal vein occlusion was administered a 1.0 mg intravitreal injection of bevacizumab in his left eye. Visual acuity prior to injection was 20/200; one week after the injection, acuity improved to 20/50 and OCT demonstrated resolution of the macular edema. Four weeks post-injection, visual acuity was 20/60 and OCT showed continued resolution of the macular edema. In both of these cases, systemic blood pressure of the patients remained stable.

**DRCR.net Protocol H Study**

In 2007, the DRCR.net reported results from a phase 2 randomized clinical trial that suggested intravitreal bevacizumab treatment had an effect on the reduction of DME in some eyes. Study eyes were randomized to one of five treatment groups: macular laser alone, 1.25 mg bevacizumab at baseline and 6 weeks, 2.5 mg bevacizumab at baseline and 6 weeks, 1.25 mg bevacizumab at baseline only, or 1.25 mg bevacizumab at baseline and 6 weeks and macular laser at 3 weeks. At three weeks, there was a reduction of OCT central subfield thickness > 11% (reliability limit) in 36 of 84 (43%) eyes treated with any bevacizumab. Compared with the eyes in the laser control group, both the 1.25 and 2.5 mg bevacizumab-treated eyes had a greater reduction in central retinal thickness at 3 weeks, although there was no statistically significant difference between the groups after the 3 week time point.

**PACORES Study**

The Pan-American Collaborative Retina Group (PACORES) also reported an apparent benefit of bevacizumab treatment for DME in a retrospective review of data from 101 eyes of 82 patients, with statistically significant improvements from baseline in best corrected visual acuity and central macular thickness that were sustained over 12 months.
**BOLT Study**

The BOLT Study (A Prospective Randomized Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema) randomized 80 eyes from 80 study participants to intravitreal bevacizumab (given q 6 weeks with a minimum of 3 injections in the first 12 months) or macular laser treatment and found that whereas the bevacizumab group gained a median of 8 letters in visual acuity over 12 months, the laser group lost a median of 0.5 letters over the same time period \( p = 0.0002 \).\(^{27}\) Central macular thickness also decreased to a greater extent in the bevacizumab as compared with the laser group (mean change + SD: \(-130 + 122\) versus \(-68 + 171\) microns).

**CATT Study**

In the Comparison of Age-related Macular Degeneration Treatments Trials (CATT), 1208 age-related macular degeneration (AMD) participants with choroidal neovascularization (CNV) in the study eye were randomly assigned to bevacizumab or ranibizumab intravitreal treatments. CATT was a non-inferiority trial design with 4 arms and a primary outcome set at 1 year follow-up, and 1107 were followed for up to 2 years. Both groups showed comparable improvements in VA scores (~8-9 ETDRS letters improvement for monthly treatments) at both 1 and 2 years. Mean reduction in total foveal thickness (in the range of 180-190 μm) was also observed to be comparable in both groups at 2 years. However, the proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab than ranibizumab (39.9% vs. 31.7%; adjusted risk ratio, 1.30; 95% CI, 1.07-1.57; \( P = 0.009 \)). Most of the excess events have not been associated previously with systemic therapy targeting VEGF.\(^{28}\) The CATT study conclusions were that ranibizumab and bevacizumab had similar effects on visual acuity over a 2-year period, with some assessments favoring ranibizumab. Treatment as needed (as opposed to a regular monthly schedule) resulted in less gain in visual acuity (~5-7 ETDRS letters) for both products, whether instituted at enrollment or after 1 year of monthly treatment. There were no differences between ranibizumab and bevacizumab in rates of death or arteriothrombotic events. The interpretation of the persistence of higher rates of serious adverse events with bevacizumab is uncertain because of the lack of specificity to conditions associated with inhibition of VEGF. CNV rates in the untreated fellow eyes of participants treated with bevacizumab in the CATT trial was not significantly different than those patients treated with ranibizumab after 2 years.\(^{29}\)

**Potential Adverse Effects with Intravitreal Bevacizumab**

In contrast to chronic high-dose (5-10 mg/kg) intravenous infusions of bevacizumab for cancer which are associated with increased risks of hypertension and thromboembolic events, a 1.25 mg intravitreal dose (400-500 fold less drug) appears much less likely to cause systemic side effects. Indeed, available data suggest that intravitreally-administered bevacizumab in substantially smaller doses (1.25 or 2.5 mg) appears to have a good safety profile with regard to ocular and systemic adverse events. No increased rates of thromboembolic events or death in bevacizumab versus control groups have been reported in smaller, prospective randomized studies including the DCRR.net Protocol H or the BOLT study. Retrospective, observational data from larger patient groups also does not appear to indicate an increased risk of ocular or systemic events with intravitreal bevacizumab treatment. In 2006, an internet-based survey of 70 international sites from 12 countries was reported that described outcomes after 7,113 injections given to 5,228 patients. Rates were 0.21% or less for each category of doctor-reported adverse events, including
blood pressure elevation, transient ischemic attack, cerebrovascular accident, death, endophthalmitis, retinal detachment, uveitis, or acute vision loss. The PACORES group reported 12 month safety of intravitreal injections of 1.25 and 2.5 mg doses of bevacizumab given for a variety of conditions in a large group of study participants including 548 patients with diabetes. A total of 1,174 patients were followed for at least 1 year. Systemic adverse events were reported in 1.5% (N = 18), including elevated blood pressure in 0.6% (7), cerebrovascular accidents in 0.5% (6), myocardial infarctions in 0.4% (5), iliac artery aneurysms in 0.2% (2), toe amputations in 0.2% (2), and deaths in 0.4% (5) of patients. The overall mortality rate of diabetic patients in this study was low at 0.55% (3/548). Ocular complications were reported as bacterial endophthalmitis in 0.2% (7), traction retinal detachments in 0.2% (7), uveitis in 0.1% (4), and a single case each of rhegmatogenous retinal detachment and vitreous hemorrhage. Recently reported results from the CATT Research Group also suggest that intravitreal bevacizumab is well tolerated. At one year, 4 of 286 participants (1.4%) in the bevacizumab group treated monthly had died and 11 of 300 participants (3.7%) in the bevacizumab given as needed group had died. Arteriothrombotic events occurred at a rate of 2.1% and 2.7% in the monthly bevacizumab and as needed bevacizumab groups, respectively. Venous thrombotic events occurred at rates of 1.4% and 0.3% in the monthly bevacizumab and as needed bevacizumab groups, respectively. Endophthalmitis occurred after 0.07% of injections in patients treated with bevacizumab. Although a higher rate of serious systemic adverse events was present in the bevacizumab group as compared with the ranibizumab group, the excess events in the bevacizumab group were primarily hospitalizations due to events not previously attributed to anti-VEGF treatment.

In 2014, a systematic review of nine non-industry-funded, randomized clinical trials (3665 participants) was conducted by the Cochrane Collaboration. Six of the trial results were published (2745 participants) and three were unpublished (920 participants). With regard to safety differences for systemic side effects, the meta-analysis indicated that no difference could be observed between intravitreal bevacizumab and intravitreal ranibizumab in the first two years of treatment for deaths, all systemic serious adverse events, and specific subsets of systemic serious adverse events with the exception of gastrointestinal disorders. The authors concluded that if a difference in systemic adverse events exists for these two drugs, that the difference is likely to be small.

Bevacizumab has been given intravitreally to many tens of thousands of patients with age-related macular degeneration or diabetic macular edema in doses generally of 1.25 or 2.5 mg per injection (a fraction of the systemic dose). There have not been consistent reports suggestive of adverse systemic effects of the drug. This seems to rule out serious systemic events being common but does not rule out the possibility of such events occurring rarely. Patients with diabetes are at increased risk for myocardial infarction, stroke, and renal disease. Thus, if a study participant develops a cardiovascular or renal problem, it may be due to the vascular effects of diabetes and other systemic factors and not related to bevacizumab. It is likely that only in a large study (much larger than what has been studied thus far) comparing adverse event rates between a bevacizumab-treated group and a control group will it be possible to determine if there is an excess of systemic adverse events with bevacizumab. At this time, it is believed that the chances of a serious systemic effect of bevacizumab are very small. However, we cannot rule out this possibility. In view of the large number of eyes treated with bevacizumab injections, it also seems unlikely that the drug has a deleterious effect on the retina or other parts of the eye.
**Potential Adverse Effects Associated with the Intravitreal Injection Procedure**

Rarely, the drugs used to anesthetize the eye before the injections (proparacaine, tetracaine, or xylocaine) can cause an allergic reaction, seizures, and an irregular heartbeat.

Subconjunctival hemorrhage or floaters will commonly occur as a result of the intravitreal injection. Mild discomfort, ocular hyperemia, increased lacrimation, discharge or itching lasting for a few days is also likely.

Immediately following the injection, there may be elevation of intraocular pressure. It usually returns to normal spontaneously, but may need to be treated with topical drugs or a paracentesis to lower the pressure. The likelihood of permanent loss of vision from elevated intraocular pressure is less than 1%.

As a result of the injection, endophthalmitis (infection in the eye) could develop. Endophthalmitis is an intraocular inflammatory process. It can be due to infection with pathogens such as bacteria of fungi or can be noninfectious. Clinical features include lid edema, conjunctival injection, corneal edema, anterior chamber and vitreous inflammation and hypopyon. Infectious endophthalmitis can occur following an intraocular procedure (i.e., cataract surgery, vitrectomy surgery, intravitreal injection), as a result of systemic infection, as a result of trauma, or occur as a late feature of conjunctival filtering blebs. The incidence and causative pathogens following intravitreal injection of bevacizumab are not well defined. At least in the published literature, this complication appears uncommon. If this occurs, it is treated by intravitreal injection of antibiotics, but there is a risk of permanent loss of vision including blindness. The risk of endophthalmitis is less than 1%.

As a result of the injection, a retinal detachment could occur. If this occurs, surgery may be needed to repair the retina. The surgery is usually successful at reattaching the retina. However, a retinal detachment can produce permanent loss of vision and even blindness. The risk of retinal detachment is less than 1%.

The injection could cause a vitreous hemorrhage. Usually the blood will resolve spontaneously, but if not, surgery may be needed to remove the blood. Although the surgery usually successfully removes the blood, there is a small risk of permanent loss of vision and even blindness. The risk of having a vitreous hemorrhage due to the injection is less than 1%.

While embryo-fetal toxicity has been observed in pregnant rabbits receiving as low as 10 mg/kg doses every 3 days during organogenesis, the dose being used for intravitreal injection is approximately 700 times lower per kg bodyweight. Toxicity testing was not conducted at such low doses, but women of reproductive potential should be advised of the potential risks, and women of reproductive potential should be advised to use effective contraception during treatment with, and for 6 months after the last dose of, bevacizumab.

**7.5 Marketing Experience**

The United States Food and Drug Administration (FDA) gave marketing approval for bevacizumab as a systemic therapy in combination with other agents for the treatment of metastatic colorectal cancer and subsequently gave marketing approval for the treatment of non-squamous non-small cell lung cancer, glioblastoma, and metastatic renal cell carcinoma. The FDA also initially granted marketing approval of bevacizumab for the treatment of metastatic breast cancer, but the agency subsequently recommended removal of the breast cancer indication from the drug’s label after an independent
advisory committee determined that the drug has not been shown to be safe and effective for that use.\textsuperscript{33} The breast cancer indication no longer appears in the FDA-approved labeling. Bevacizumab in combination with other agents is approved in the European Union (EU) for the treatment of metastatic colorectal cancer, breast cancer, non-small cell lung cancer, renal cell cancer, and advanced ovarian cancer.\textsuperscript{34} Bevacizumab is not currently marketed for intraocular use in any country, although off-label use continues to grow.

\begin{itemize}
\item \textsuperscript{24} Rosenfeld PJ MA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmic Surg Lasers Imaging. 2005;36(331-335).
\end{itemize}


8.0 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

VEGF is a major regulator of angiogenesis and vascular permeability during normal and pathological processes, including tumor growth and retinal-pathologies. Bevacizumab selectively binds with high affinity to all isoforms of human VEGF-A. When injected into the vitreous, bevacizumab exhibits a half-life of 4-6 days in rabbits, and over 9 days in humans. Intravitreal bevacizumab has been observed in studies to improve visual acuity and reduce retinal thickening associated with several retinal pathologies, including CRVO.

Significant clinical experience has been reported with off-label use of intravitreal bevacizumab for several indications, including prospective studies in the US and abroad. With hundreds of thousands of intravitreal doses being delivered annually, the potential for both systemic and ocular adverse events cannot be dismissed. However, reports of systemic adverse events following intravitreal bevacizumab are rare.

The greatest potential risk for ocular adverse events appears to be associated with the intravitreal injection procedure itself. The most serious types include endophthalmitis, retinal detachments, uveitis, and vitreous hemorrhage. While these are potentially serious ocular events, they have so far been observed to occur at relatively low frequencies (≤ 0.2%). Subconjunctival hemorrhage or floaters will commonly occur as a result of the intravitreal injection. Mild discomfort, ocular hyperemia, increased lacrimation, and ocular discharge or itching lasting for a few days are also likely.

SCORE2 investigators should approach intravitreal bevacizumab injections with the same care and diligence as is necessary for any penetrating ocular treatment. Investigators must observe sterile technique scrupulously and following the protocol-specified injection procedures closely. SCORE2 study participants need to be followed as described in the protocol to observe for any adverse events, and, should they occur, treatment-emergent adverse events should be reported and treated as medically indicated.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OZURDEX® safely and effectively. See full prescribing information for OZURDEX®.

OZURDEX® (dexamethasone intravitreal implant)
For Intravitreal Injection
Initial U.S. Approval: 1958

RECENT MAJOR CHANGES
- Indications and Usage (1.3) 9/2014
- Contraindications (4.2, 4.3, 4.4) 9/2014
- Warnings and Precautions (5.2) 9/2014

INDICATIONS AND USAGE
OZURDEX® is a corticosteroid indicated for:
- The treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) (1.1)
- The treatment of non-infectious uveitis affecting the posterior segment of the eye (1.2)
- The treatment of diabetic macular edema (1.3)

DOSAGE AND ADMINISTRATION
- For ophthalmic intravitreal injection. (2.1)
- The intravitreal injection procedure should be carried out under controlled aseptic conditions. (2.2)
- Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. (2.2)

DOSAGE FORMS AND STRENGTHS
Intravitreal implant containing dexamethasone 0.7 mg in the NOVADUR® solid polymer drug delivery system. (3)

CONTRAINDICATIONS
- Ocular or periocular infections (4.1)
- Glaucoma (4.2)
- Torn or ruptured posterior lens capsule (4.3)
- Hypersensitivity (4.4)

WARNINGS AND PRECAUTIONS
- Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection. (5.1)
- Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. (5.2)

ADVERSE REACTIONS
In controlled studies, the most common adverse reactions reported by 20–70% of patients were cataract, increased intraocular pressure and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

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2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
2.2 Administration
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4.1 Ocular or Periocular Infections
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Retinal Vein Occlusion
OZURDEX® (dexamethasone intravitreal implant) is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

1.2 Posterior Segment Uveitis
OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

1.3 Diabetic Macular Edema
OZURDEX® is indicated for the treatment of diabetic macular edema.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information
For ophthalmic intravitreal injection.

2.2 Administration
The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide applied to the periocular skin, eyelid and ocular surface are recommended to be given prior to the injection.

Remove the foil pouch from the carton and examine for damage. Then, open the foil pouch over a sterile field and gently drop the applicator on a sterile tray. Carefully remove the cap from the applicator. Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab. The long axis of the applicator should be held parallel to the limbus, and the sclera should be engaged at an oblique angle with the bevel of the needle up (away from the sclera) to create a shelved scleral path. The tip of the needle is advanced within the sclera for about 1 mm (parallel to the limbus), then re-directed toward the center of the eye and advanced until penetration of the sclera is completed and the vitreous cavity is entered. The needle should not be advanced past the point where the sleeve touches the conjunctiva.

Slowly depress the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully depressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous.

Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each applicator can only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new applicator must be used, and the sterile field, syringe, gloves, drapes, and eyelid speculum should be changed before OZURDEX® is administered to the other eye.

3 DOSAGE FORMS AND STRENGTHS
Intravitreal implant containing dexamethasone 0.7 mg in the NOVADUR® solid polymer drug delivery system.
4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

4.2 Glaucoma
OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

4.3 Torn or Ruptured Posterior Lens Capsule
OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

4.4 Hypersensitivity
OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product [see Adverse Reactions (6)].

5 WARNINGS AND PRECAUTIONS
5.1 Intravitreal Injection-related Effects
Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection [see Patient Counseling Information (17)].

5.2 Steroid-related Effects
Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses [see Adverse Reactions (6.1)].

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions associated with ophthalmic steroids including OZURDEX® include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Retinal Vein Occlusion and Posterior Segment Uveitis
The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):
Table 1: Adverse Reactions Reported by Greater than 2% of Patients

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>OZURDEX® N=497 (%)</th>
<th>Sham N=498 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular pressure increased</td>
<td>125 (25%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>108 (22%)</td>
<td>79 (16%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>40 (8%)</td>
<td>26 (5%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>33 (7%)</td>
<td>27 (5%)</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>23 (5%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>24 (5%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>12 (2%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (4%)</td>
<td>12 (2%)</td>
</tr>
</tbody>
</table>

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Following a second injection of OZURDEX® in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

Diabetic Macular Edema

The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in Table 2 were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are shown in Tables 2 and 3:

Table 2: Ocular Adverse Reactions Reported by ≥1% of Patients and Non-ocular Adverse Reactions Reported by ≥5% of Patients

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>OZURDEX® N=324 (%)</th>
<th>Sham N=328 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract¹</td>
<td>166/243= (68%)</td>
<td>49/230 (21%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>73 (23%)</td>
<td>44 (13%)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>28 (9%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>19 (6%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>16 (5%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>15 (5%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>15 (5%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>14 (4%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vitreous opacities</td>
<td>11 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Retinal aneurysm</td>
<td>10 (3%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>7 (2%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Corneal erosion</td>
<td>7 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>6 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
<td>6 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Retinal tear</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td><strong>Non-ocular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (13%)</td>
<td>21 (6%)</td>
</tr>
</tbody>
</table>
Increased Intraocular Pressure

Table 3: Summary of Elevated Intraocular Pressure (IOP) Related Adverse Reactions

<table>
<thead>
<tr>
<th>IOP</th>
<th>Treatment: N (%)</th>
<th>OZURDEX® N=324</th>
<th>Sham N=328</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP elevation ≥10 mm Hg from Baseline at any visit</td>
<td>91 (28%)</td>
<td>13 (4%)</td>
<td></td>
</tr>
<tr>
<td>≥30 mm Hg IOP at any visit</td>
<td>50 (15%)</td>
<td>5 (2%)</td>
<td></td>
</tr>
<tr>
<td>Any IOP lowering medication</td>
<td>136 (42%)</td>
<td>32 (10%)</td>
<td></td>
</tr>
<tr>
<td>Any surgical intervention for elevated IOP *</td>
<td>4 (1.2%)</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
</tbody>
</table>

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization, 1 laser iridotomy, 1 surgical iridectomy
Sham: 1 laser iridotomy

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period) shown below:

Figure 1: Mean IOP during the study

Cataracts and Cataract Surgery

At baseline, 243 of the 324 OZURDEX® subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.
6.2 Postmarketing Experience
The following reactions have been identified during post-marketing use of OZURDEX® in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to OZURDEX®, or a combination of these factors, include: complication of device insertion (implant misplacement), device dislocation with or without corneal edema, endophthalmitis, hypotony of the eye (associated with vitreous leakage due to injection), and retinal detachment.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
Risk Summary
There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Animal reproduction studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed. OZURDEX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 3 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis.

8.3 Nursing Mothers
Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of dexamethasone following intravitreal treatment with OZURDEX® is low [see Clinical Pharmacology (12.3)]. It is not known whether intravitreal treatment with OZURDEX® could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when OZURDEX® is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness of OZURDEX® in pediatric patients have not been established.

8.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION
OZURDEX® is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the NOVADUR® solid polymer sustained-release drug delivery system. OZURDEX® is preloaded into a single-use, DDS® applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The NOVADUR® system contains poly (D,L-lactide-co-glycolide) PLGA intravitreal polymer matrix without a preservative. The chemical name for dexamethasone is Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11β,16α)-. Its structural formula is:
Dexamethasone occurs as a white to cream-colored crystalline powder having not more than a slight odor, and is practically insoluble in water and very soluble in alcohol.

The PLGA matrix slowly degrades to lactic acid and glycolic acid.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Dexamethasone, a corticosteroid, has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines resulting in decreased edema, fibrin deposition, capillary leakage and migration of inflammatory cells.

12.3 Pharmacokinetics
Plasma concentrations were obtained from 21 patients with macular edema due to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), and 21 patients with diabetic macular edema (DME) prior to dosing and at 4 to 5 additional post-dose timepoints on Days 1, 7, 21, 30, 45, 60, and 90 following the administration of the first intravitreal implant containing 0.7 mg dexamethasone. In RVO and DME patients, the majority of plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ = 50 pg/mL). Plasma dexamethasone concentrations from 12% of samples were above the LLOQ, ranging from 52 pg/mL to 102 pg/mL. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In an in vitro metabolism study, following the incubation of [14C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humor, and sclera tissues for 18 hours, no metabolites were observed.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No adequate studies in animals have been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of OZURDEX®, dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells in vitro or in the in vivo mouse micronucleus test.

Adequate fertility studies have not been conducted in animals.

14 CLINICAL STUDIES

Retinal Vein Occlusion
The efficacy of OZURDEX® for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) was assessed in two, multicenter, double-masked, randomized, parallel studies.
Following a single injection, OZURDEX® demonstrated the following clinical results for the percent of patients with $\geq 15$ letters of improvement from baseline in best-corrected visual acuity (BCVA):

Table 4: Number (Percent) of Patients with $\geq 15$ Letters Improvement from Baseline in BCVA

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study 1</th>
<th>p-value*</th>
<th>Study 2</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OZURDEX®</td>
<td>Sham</td>
<td></td>
<td>OZURDEX®</td>
</tr>
<tr>
<td></td>
<td>N=201</td>
<td>N=202</td>
<td></td>
<td>N=226</td>
</tr>
<tr>
<td>Day 30</td>
<td>40 (20%)</td>
<td>15 (7%)</td>
<td>$&lt; 0.01$</td>
<td>51 (23%)</td>
</tr>
<tr>
<td>Day 60</td>
<td>58 (29%)</td>
<td>21 (10%)</td>
<td>$&lt; 0.01$</td>
<td>67 (30%)</td>
</tr>
<tr>
<td>Day 90</td>
<td>45 (22%)</td>
<td>25 (12%)</td>
<td>$&lt; 0.01$</td>
<td>48 (21%)</td>
</tr>
<tr>
<td>Day 180</td>
<td>39 (19%)</td>
<td>37 (18%)</td>
<td>0.780</td>
<td>53 (24%)</td>
</tr>
</tbody>
</table>

*p-values were based on the Pearson’s chi-square test.

In each individual study and in a pooled analysis, time to achieve $\geq 15$ letters (3-line) improvement in BCVA cumulative response rate curves were significantly faster with OZURDEX® compared to sham ($p < 0.01$), with OZURDEX® treated patients achieving a 3-line improvement in BCVA earlier than sham-treated patients.

The onset of a $\geq 15$ letter (3-line) improvement in BCVA with OZURDEX® occurs within the first two months after implantation in approximately 20-30% of subjects. The duration of effect persists approximately one to three months after onset of this effect.

**Posterior Segment Uveitis**

The efficacy of OZURDEX® was assessed in a single, multicenter, masked, randomized study of 153 patients with non-infectious uveitis affecting the posterior segment of the eye.

After a single injection, the percent of patients reaching a vitreous haze score of 0 (where a score of 0 represents no inflammation) was statistically significantly greater for patients receiving OZURDEX® versus sham at week 8 (primary time point) (47% versus 12%). The percent of patients achieving a 3-line improvement from baseline BCVA was 43% for patients receiving OZURDEX® versus 7% for sham at week 8.

**Diabetic Macular Edema**

The efficacy of OZURDEX® for the treatment of diabetic macular edema was assessed in two, multicenter, masked, randomized, sham-controlled studies. Subjects were to be evaluated for retreatment eligibility every three months starting from Month 6 but could only receive successive treatments at least 6 months apart. Retreatment was based on physician’s discretion after examination including Optical Coherence Tomography. Patients in the OZURDEX® arm received an average of 4 treatments during the 36 months.

The primary endpoint was the proportion of patients with 15 or more letters improvement in BCVA from baseline at Month 39 or final visit for subjects who exited the study at or prior to Month 36. The Month 39 extension was included to accommodate the evaluation of safety and efficacy outcomes for subjects who received re-treatment at Month 36. Only fourteen percent of the study patients completed the Month 39 visit (16.8% from OZURDEX® and 12.2% from Sham).
Table 5: Visual Acuity outcomes at Month 39 (All randomized subjects with LOCF\textsuperscript{c})

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>OZURDEX\textsuperscript{\textregistered}</th>
<th>Sham</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{a}</td>
<td>Mean (SD) Baseline BCVA (Letters)</td>
<td>56 (10)</td>
<td>57 (9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (range) Baseline BCVA (Letters)</td>
<td>59 (34-95)</td>
<td>58 (34-74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gain of $\geq 15$ letters in BCVA (n(%))</td>
<td>34 (21%)</td>
<td>19 (12%)</td>
<td>$9.3%$ (1.4%, 17.3%)</td>
</tr>
<tr>
<td></td>
<td>Loss of $\geq 15$ letters in BCVA (n(%))</td>
<td>15 (9%)</td>
<td>17 (10%)</td>
<td>$-1.1%$ (-7.5%, 5.3%)</td>
</tr>
<tr>
<td></td>
<td>Mean change in BCVA (SD)</td>
<td>4.1 (13.9)</td>
<td>0.9 (11.9)</td>
<td>$3.2$ (0.4, 5.9)</td>
</tr>
<tr>
<td>2\textsuperscript{b}</td>
<td>Mean (SD) Baseline BCVA (Letters)</td>
<td>55 (10)</td>
<td>56 (9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (range) Baseline BCVA (Letters)</td>
<td>58 (34-72)</td>
<td>58 (36-82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gain of $\geq 15$ letters in BCVA (n(%))</td>
<td>30 (18%)</td>
<td>16 (10%)</td>
<td>$8.4%$ (0.9%, 15.8%)</td>
</tr>
<tr>
<td></td>
<td>Loss of $\geq 15$ letters in BCVA (n(%))</td>
<td>30 (18%)</td>
<td>18 (11%)</td>
<td>$7.1%$ (-0.5%, 14.7%)</td>
</tr>
<tr>
<td></td>
<td>Mean change in BCVA (SD)</td>
<td>0.4 (17.5)</td>
<td>0.8 (13.6)</td>
<td>$-0.7$ (-4.1, 2.6)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Study 1: OZURDEX\textsuperscript{\textregistered}, N=163; Sham, N=165

\textsuperscript{b}Study 2: OZURDEX\textsuperscript{\textregistered}, N=165; Sham, N=163

\textsuperscript{c}14\% (16.8\% from OZURDEX\textsuperscript{\textregistered} and 12.2\% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients, the data at Month 36 or earlier was carried forward.

Visual acuity outcomes by lens status (Phakic or Pseudophakic) at different visits are presented in Figure 2 and Figure 3. The occurrence of cataracts impacted visual acuity during the study. The visual acuity improvement from baseline increases during a treatment cycle, peaks at approximately 3 Months posttreatment and diminishes thereafter. Patients who were pseudophakic at baseline achieved greater mean BCVA change from baseline at the final study visit.
Figure 2: Proportion of Subjects with $\geq 15$ Letters Improvement from Baseline BCVA in the Study Eye
The best corrected visual acuity outcomes for the Pseudophakic and Phakic subgroups from Studies 1 and 2 at Month 39 are presented in Table 6.

### Table 6: Visual Acuity outcomes at Month 39 (Subgroup for pooled data with LOCF)

<table>
<thead>
<tr>
<th>Subgroup (Pooled)</th>
<th>Outcomes</th>
<th>OZURDEX® (n(%))</th>
<th>Sham (n(%))</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>aPseudophakic</strong></td>
<td><strong>Gain of ≥15 letters in BCVA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n(%))</td>
<td>16 (20%)</td>
<td>11 (11%)</td>
<td>8.4% (-2.2%, 19.0%)</td>
</tr>
<tr>
<td></td>
<td><strong>Loss of ≥15 letters in BCVA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n(%))</td>
<td>4 (5%)</td>
<td>7 (7%)</td>
<td>-2.2% (-9.1%, 4.7%)</td>
</tr>
<tr>
<td></td>
<td><strong>Mean change in BCVA (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n(%))</td>
<td>5.8 (11.6)</td>
<td>1.4 (12.3)</td>
<td>4.2 (0.8, 7.6)</td>
</tr>
<tr>
<td><strong>bPhakic</strong></td>
<td><strong>Gain of ≥15 letters in BCVA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n(%))</td>
<td>48 (20%)</td>
<td>24 (11%)</td>
<td>9.0% (2.7%, 15.4%)</td>
</tr>
<tr>
<td></td>
<td><strong>Loss of ≥15 letters in BCVA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n(%))</td>
<td>41 (17%)</td>
<td>28 (12%)</td>
<td>4.4% (-1.9%, 10.7%)</td>
</tr>
<tr>
<td></td>
<td><strong>Mean change in BCVA (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n(%))</td>
<td>1.0 (16.9)</td>
<td>0.6 (12.9)</td>
<td>0.3 (-2.4, 3.0)</td>
</tr>
</tbody>
</table>

- **a** Pseudophakic: OZURDEX®, N=82; Sham, N=99
- **b** Phakic: OZURDEX®, N=246; Sham, N=229
- **c** 14% (16.8% from OZURDEX® and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients the data at Month 36 or earlier was used in the analysis.
16 HOW SUPPLIED/STORAGE AND HANDLING

OZURDEX® (dexamethasone intravitreal implant) 0.7 mg is supplied in a foil pouch with 1 single-use plastic applicator, NDC 0023-3348-07.

Storage: Store at 15º-30ºC (59º-86ºF).

17 PATIENT COUNSELING INFORMATION

Steroid-related Effects
Advise patients that a cataract may occur after repeated treatment with OZURDEX®. If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with OZURDEX® treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

Intravitreal Injection-related Effects
Advise patients that in the days following intravitreal injection of OZURDEX®, patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

When to Seek Physician Advice
Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines
Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

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