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SCORE2 Report 2: Study Design and Baseline Characteristics

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Abstract

Objectives—To describe the design and baseline characteristics of participants in the ***S***tudy of ***CO***mparative Treatments for ***RE***tinal Vein Occlusion 2 (SCORE2) and to compare with cohorts from other retinal vein occlusion trials.

Design—Phase III prospective multicenter randomized clinical trial designed to assess whether intravitreal bevacizumab is non-inferior to intravitreal aflibercept for treatment of decreased vision attributable to macular edema due to central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO).

Participants—362 participants, including 307 with CRVO and 55 with HRVO.

Methods—Demographic and study eye characteristics are summarized and compared between CRVO and HRVO study participants.

Main outcome measures—Baseline ophthalmic characteristics, including visual acuity and retinal thickness, and medical history characteristics, including hypertension, diabetes mellitus, and coronary artery disease.

Results—The mean age of participants was 69 years, 76% of participants were white, and 90% were non-Hispanic. There was a racial disparity with respect to disease type, with 38% of HRVO patients being black compared to 11% of CRVO patients (p-value adjusted for multiple testing=0.0001). This is similar to findings from the previous SCORE Study. Comorbidities

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included hypertension (77%), diabetes mellitus (31%) and coronary artery disease (15%). At baseline, mean visual acuity letter score (VALS) was 50 (20/100) (range: 19–73; 20/400-20/40), mean optical coherence tomography-measured central subfield thickness (OCT-CST) was 678 microns (range: 300–1203), and mean number of months from diagnosis of macular edema to randomization was 6 (range: 0–104). One hundred twenty (33%) SCORE2 participants had been treated previously with anti-VEGF therapy, with these participants having baseline VALS and OCT-CST similar to those without prior anti-VEGF treatment, but longer mean duration of macular edema before randomization (18 months versus 1 month for those without prior anti-VEGF treatment; $p<0.0001$).

Conclusions—The SCORE2 cohort is a heterogeneous population, including both CRVO and HRVO eyes and both treatment-naive eyes and eyes treated previously with anti-VEGF, which will allow study results to have broad applicability to CRVO and HRVO patients receiving treatment for macular edema. Similarities of the baseline characteristics of the SCORE2 population to other CRVO trial cohorts will allow meaningful comparisons of outcome results across trials.

INTRODUCTION

Retinal vein occlusion is the most common retinal vascular disorder after diabetic retinopathy, affecting 1–2% of the population older than 40 years,[1,2] and 16 million persons worldwide.[3] Macular edema is the most frequent cause of vision loss in patients with retinal vein occlusion.[4–6] While many treatment options have been investigated for decreased vision attributable to macular edema due to central retinal vein occlusion (CRVO),[7–16] the ***S***tandard Care versus ***CO***rticosteroid for ***RE***tinal Vein Occlusion (SCORE) Study, sponsored by the National Eye Institute (NEI), was the first phase III clinical trial to demonstrate that a therapy could favorably alter the visual outcomes of CRVO-associated macular edema. The SCORE Study demonstrated that intravitreal injection(s) of triamcinolone acetonide was superior to standard care established by the Central Vein Occlusion Study[7] (i.e., observation) for vision loss associated with macular edema secondary to CRVO.[17] Subsequently, several industry-sponsored phase III trials demonstrated the efficacy of anti-vascular endothelial growth factor (anti-VEGF) therapy in the treatment of decreased vision due to CRVO-associated macular edema; the CRUISE[18] Study demonstrated favorable visual outcomes associated with the use of intravitreal ranibizumab, and the COPERNICUS[19] and GALILEO[20] Studies demonstrated favorable visual outcomes associated with the use of intravitreal aflibercept. In addition, numerous case reports and small randomized clinical trials of favorable visual acuity outcomes following intravitreal bevacizumab in patients with decreased vision attributable to macular edema secondary to CRVO were published.[15, 21–30]

The Food and Drug Administration (FDA) approved Ozurdex (Allergan Pharmaceuticals, Inc., Irvine, CA), an intravitreal dexamethasone implant, for treatment of macular edema associated with RVO in 2009.[31] However, it is not commonly used as a first-line therapy for RVO-associated macular edema due to the higher reported rates of ocular adverse events, such as intraocular pressure elevation and cataract, associated with the dexamethasone implant than with anti-VEGF agents.[18–20, 31, 32, 33]

Ranibizumab (an antibody fragment) and bevacizumab (a full-length antibody) inhibit all VEGF-A isoforms, and have demonstrated similar efficacy and safety in the treatment of age-related macular degeneration (AMD) [32] and diabetic macular edema (DME).[34] Aflibercept, a fusion protein of key domains from both VEGF receptor 1 and VEGF receptor 2, includes inhibition of not only all VEGF-A isoforms, but also VEGF-B and placental derived growth factor.[35] In addition to its broader mechanism of action, aflibercept has been reported to have a higher binding affinity than ranibizumab.[32, 35] Bevacizumab repackaged at compounding pharmacies into syringes for treatment of CRVO is much less costly, at approximately $60 per dose[36], compared with either ranibizumab ($1950/dose) or aflibercept ($1850/dose).[37] SCORE2 is designed to determine if bevacizumab is non-inferior to aflibercept for the treatment of macular edema secondary to CRVO. In addition, SCORE2 is designed to investigate whether the frequency of intravitreal injections can be reduced in eyes that have responded well to anti-VEGF treatment (reduced injection frequency 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 (a different anti-VEGF agent or intravitreal dexamethasone) in eyes that have not responded well to an anti-VEGF agent.

STUDY DESIGN AND METHODS

Study Synopsis

SCORE2 is a multicenter, prospective, randomized, phase III clinical trial designed to determine if bevacizumab is non-inferior to aflibercept for the treatment of decreased vision due to macular edema associated with CRVO. The primary efficacy outcome of this study is change in Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity letter score from the randomization visit to the Month 6 follow-up visit. The non-inferiority margin is set at an ETDRS visual acuity letter score of 5 as measured by the electronic ETDRS visual acuity test (E-ETDRS). Secondary efficacy outcomes are based on visual acuity testing, spectral domain optical coherence tomography (SD-OCT), fundus photography, ultra-widefield fluorescein angiography, and quality of life as measured by the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25)[38] and safety outcomes include both ocular and systemic events, as listed in Table 1. Study participants are followed for 1 year after randomization. SCORE2 is registered on http://www.clinicaltrials.gov (identifier: NCT01969708).

The target sample size was 360 patients. Study eyes were randomized in a 1:1 ratio to intravitreal bevacizumab (1.25 mg) every 4 weeks versus intravitreal aflibercept (2.0 mg) every 4 weeks. The primary non-inferiority comparison between the 2 groups is performed at Month 6. Following assessment of the primary outcome at Month 6, SCORE2 used an adaptive treatment strategy in which participants assigned at baseline to aflibercept who meet the protocol-defined criteria for a good response were re-randomized to either continuing aflibercept every 4 weeks versus changing to a treat and extend (TAE) regimen with monthly assessment. Participants assigned at baseline to bevacizumab who met the protocol-defined criteria for a good response were re-randomized to either continuing bevacizumab every 4 weeks versus changing to a TAE regimen. This allowed 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 received aflibercept. Participants originally assigned to aflibercept with a protocol-defined poor or marginal response at Month 6 received rescue therapy with a dexamethasone implant. Rescue therapy with bevacizumab for these patients was not part of the protocol, since it was deemed more likely that participants who are failures to aflibercept, with its broad mechanism of action, will more likely respond to a dexamethasone implant. An abbreviated description of the SCORE2 design and methods is given herein; a full description is provided elsewhere.[39]

Participating study personnel such as physician-investigators and study coordinators were certified by the Data Coordinating Center (DCC) (The Emmes Corporation, Rockville, MD) before they could participate in this study. All physician-investigators were board-certified in ophthalmology and had completed a retina fellowship. Technicians who performed visual acuity testing and refraction were certified by Ophthalmic Clinical Trial Training and Certification (OCTTC) (The Emmes Corporation, Rockville, MD). Photographers performing fluorescein angiograms were trained and certified by Optos (Scotland, UK), and photographers and technicians who performed the fundus photographs and OCT images for this study were certified by the University of Wisconsin Fundus Photograph Reading Center (Reading Center) before they could participate in this study.

The SCORE2 protocol and informed consent were approved by the respective clinical center institutional review boards or a centralized institutional review board. Investigators at 66 clinical centers randomized and followed SCORE2 participants in accordance with the study protocol and Manual of Policies and Procedures. Men and women at least 18 years of age could each contribute at most one study eye. Table 2 summarizes the major ocular inclusion and exclusion criteria.

Screening and Primary Randomization

Prospective participants were first consented for screening, then interviewed to obtain demographic information and medical history, including ocular history and current medications. The following screening examinations were required within 21 days of randomization: (1) IOP of both eyes by Goldmann applanation tonometry or a Tonopen; (2) ophthalmic examination including dilated ophthalmoscopy and slit-lamp examination (for lens assessment, modified Age-Related Eye Disease Study [AREDS] grading was used); (3) ultra-widefield fluorescein angiography (FA) at sites with an Optos ultra-widefield model 200Tx camera; (4) NEI VFQ- 25[38]; (5) blood pressure measurement; and (6) height and weight measurements. The following screening examinations were required within 8 days of initial randomization: measurement of visual acuity and manifest refraction, using electronic E-ETDRS visual acuity at 3 meters by a SCORE2 certified technician; (2) modified 3-field stereoscopic color fundus photographs; (3) SD-OCT; and (4) for women of childbearing potential, a urine pregnancy test. All imaging tests (color fundus photographs, FA and SD-OCT) were sent to the Reading Center. For SD-OCT, Reading Center accepted scans from both the Heidelberg and Zeiss manufacturers.

Once all eligibility criteria were met, and following informed consent for randomization, the eligible eye of each participant was randomized via a secure Internet-based central system, maintained at the DCC, to one of two equally-sized treatment arms: (1) intravitreal bevacizumab (1.25 mg) every 4 weeks or (2) intravitreal aflibercept (2.0 mg) every 4 weeks. Randomization was 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 randomized into SCORE2 was chosen by the physician and patient.

The injection protocol for intravitreal bevacizumab and intravitreal aflibercept administration is described in detail elsewhere[39] and is described briefly below. The 40 mg/mL aflibercept study drug (EYLEA®) was provided in single dose vials by Regeneron Pharmaceuticals, Inc. for 0.05 mL intravitreal injections. The bevacizumab study drug was repackaged from the original commercial product (AVASTIN®) made by Genentech, Inc. into smaller sterile 2 mL vials by the University of Pennsylvania Investigational Drug Service. The vials contained 0.1 mL (0.05 mL minimum withdrawable volume) of 25 mg/mL bevacizumab. For dexamethasone, the commercially-available intravitreal implant product (OZURDEX®) 0.7 mg was supplied by Allergan, Inc. in a foil pouch in its original box, with a single-use applicator.

Participant Visit Schedule and Secondary Randomization

Once randomized, all participants were expected to be followed for 1 year. Study visits were scheduled every 4 weeks for 6 months following randomization (see Table 3). At Month 6, the primary outcome was assessed, after which study eyes were categorized into one of two groups (1. poor or marginal response; 2. good response) based on response to treatment. Poor or marginal response was defined as 1) visual acuity letter score less than 58 letters (less than 20/80) or a visual acuity letter score improvement of 5 or less from baseline with at least some of the visual acuity deficit attributed by the investigator to macular edema secondary to CRVO; and 2) OCT had one or more of the following: retinal thickness (defined as a central subfield thickness of 300 um or greater, or 320 um or greater if the OCT measurement is taken from a Heidelberg Spectralis Machine), presence of intraretinal cystoid spaces, subretinal fluid. All eyes that did not meet the criteria for poor or marginal response were considered to have a good response. (Note that response type is not the same as primary outcome.) For the study eyes with a good response, a secondary 1:1 randomization occurred, with assignment to either: 1) six q4 week injections (from Month 6 to Month 11) with the original treatment assignment (either bevacizumab or aflibercept) or 2) TAE regimen with the originally assigned treatment (either bevacizumab or aflibercept), with each subsequent interval between visits increased by 2 weeks if the patient does well. Intervals between visits could be extended to a maximum of 10 weeks. Eyes with retinal thickness (as defined above), intraretinal cystoid spaces, or subretinal fluid on OCT were to be retreated and brought back in 4 weeks. Study eyes with a poor or marginal response were to receive rescue therapy. Eyes in the bevacizumab arm were to receive aflibercept at Months 6, 7, 8 and then on a TAE regimen. Eyes in the aflibercept arm were to receive intravitreal

dexamethasone implant at Month 6 and then pro re nata (PRN) at Month 9, 10 or 11. Secondary outcomes were assessed at Month 12.

Testing Procedures at Follow-up Visits

At each study follow-up visit, participants had E-ETDRS testing in each eye, IOP measurement in each eye, slit-lamp and dilated funduscopic examinations on each eye, and OCT imaging of the study eye. At Month 6 and Month 12, the visual acuity examiner and OCT technician were required to be masked to treatment assignment. Prior to each study injection, a urine pregnancy test was performed for all women of childbearing potential. Modified 3-field stereoscopic color fundus photographs of the study eye, lens assessment for cataract (using modified AREDS standard lens photographs) in the study eye, blood pressure measurement, NEI VFQ-25, and ultra-widefield fluorescein angiography (at selected sites) of both eyes were performed at Month 6 and Month 12.

Intravitreal Injection Procedure

On the day of injection, topical antibiotic drops could be administered to the study eye at investigator discretion. A drop of topical anesthesia was applied to the study eye. Additional anesthesia was at the discretion of the investigator. Asepsis was achieved by either application of two to three drops of 5% povidone-iodine in the lower fornix and use of a cotton-tipped applicator soaked in 5% povidone-iodine applied to the conjunctiva over the intended injection site and allowed to dry for 30–60 seconds, or use of either a cotton-tipped applicator soaked in 5% povidone-iodine or a 10% povidone-iodine Swabstick applied to the intended injection site (scrubbing the upper and lower eyelid margins and eyelashes was optional). A sterile eyelid speculum was used to separate the eyelids.

Following the preparation procedure, either 1.25 mg bevacizumab, 2.0 mg aflibercept, or an intravitreal dexamethasone implant was injected into the vitreous cavity via the pars plana 3–4 mm posterior to the limbus. The eyelid speculum was removed and indirect ophthalmoscopy was performed to confirm the intravitreal location of the dexamethasone implant (if applicable) and to confirm that the central retinal artery was perfused. A topical antibiotic could be administered post-injection at investigator discretion.

Statistical Methods

The primary efficacy outcome of this study is change in visual acuity letter score from the randomization visit to the 6-month follow-up visit. A 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 time series in which each 6M outcome is correlated with its corresponding baseline measure, which is modeled as being the same in both groups. The non-inferiority test involves testing the null hypothesis of $\beta \leq -M$ versus the alternative of $\beta > -M$, where $M=5$ is the non-inferiority margin and β , the treatment effect, estimates the visual acuity change from baseline in the treated group minus the visual acuity change from baseline in the control group. Interim testing is carried out using the Lan-DeMets[40] interim monitoring boundary with a one-tailed level 0.025 O'Brien-Fleming-type spending function, adapted for non-inferiority testing. Sample size re-estimation was also performed (before any interim monitoring) after about half the total expected number of participants attained their 6-month

outcome. This was carried out by the perturbed unblinding method,[41] under which the variance structure of the data is revealed, while the treatment effect is obscured.

In Tables 4–5, demographic and study eye characteristics are summarized and compared between treatment arms to assess the success of the randomization process in creating comparable groups, as well as to compare the characteristics of study eyes and participants with respect to disease type, CRVO and HRVO, and whether the study had anti-VEGF treatment prior to randomization. Chi-square tests were used for categorical variables, and t-tests for continuous variables. No formal multiplicity adjustment to compare randomized treatment groups was performed, since the aim is to indict the randomization procedure if there is even moderately convincing evidence that it performed incorrectly. However, family wide error was controlled in the multiple-testing setting of Tables 4 and 5 when comparing disease types (CRVO versus HRVO) and prior-versus-no-prior anti-VEGF groups. This was accomplished by adjusting p-values using Hochberg's sequentially-rejective method[42] for the disease-type and prior-type p-values, combined across Tables 4 and 5. To identify significant results, P-values that are less than 0.05, either before adjustment (comparing treatment groups) or after adjustment (comparing CRVO versus HRVO or prior versus no prior anti-VEGF therapy) are highlighted in Tables 4 and 5.

RESULTS

Between September 2014 and November 2015, 362 subjects were enrolled in SCORE2. The mean age of participants in SCORE2 was 69 years, 43% were women, 76% of participants were white, 15% black, and 10% Hispanic. The mean visual acuity letter score was 50 (20/100), and participants had macular edema for an average of 6 months before randomization. The mean SD-OCT-measured central subfield thickness was 678 microns, 33% had received prior anti-VEGF treatment and 15% of the population had a HRVO as diagnosed by the Investigator at the SCORE2 clinical center and defined as an eye that has retinal hemorrhage or other biomicroscopic evidence of retinal vein occlusion (e.g., telangiectatic capillary bed and/or dilated venous system or previously dilated venous system) in 5 or more clock hours but less than all 4 quadrants. Approximately 27% of the study eyes had a cataract extraction at randomization and only 17% had no history of a cataract. Co-morbid conditions included diabetes (31%, type 2 in all but one patient), hypertension (77%), and coronary artery disease (15%). The mean baseline NEI-VFQ-25 overall composite score is 77. When comparing the treatment groups, only one test was significant (t-test for duration of macular edema prior to study enrollment, aflibercept = 8 months, bevacizumab = 5 months, unadjusted p = 0.03). No other demographic, study eye, or clinical characteristic differed significantly between the treatment arms. Considering that 29 tests went into the construction of the treatment-group comparisons, this is roughly the number of significant outcomes we might expect by chance even if there are no differences between groups. Note also that the chi-squared test for duration of macular edema prior to study enrollment is not significant. We ascribe this nominally significant outcome to type I error, and conclude that this pattern of p-values is consistent with the treatment groups being similar. In contrast to the treatment-group comparisons, there are two significant baseline disease-type comparisons and two significant baseline prior-versus-no prior anti-VEGF

treatment comparisons, even after p- value adjustment by Hochberg's method; these comparisons are described below.

Comparison of HRVO to CRVO Eyes

The racial distribution differed between HRVO and CRVO patients, with 38% of participants with HRVO being black compared with 11% of CRVO participants (adjusted chi-squared p=0.0001, Table 4). Area of intraretinal and/or subretinal hemorrhage within the grid based on fundus photography is larger in CRVO than HRVO eyes (total area of blood > 50% of grid in 21% of CRVO eyes compared with 7% of HRVO eyes; adjusted chi-squared p = 0.04, Table 5). Note that one participant in SCORE2 was mistakenly randomized as a CRVO participant but actually had BRVO. This participant remains in the study and, for purposes of analyses, was included in the CRVO group. There was 98% agreement between investigators and the SCORE2 Reading Center on the diagnosis of CRVO, and 70% agreement on the diagnosis of HRVO (Table 5).

Comparison of Study Eyes With and Without Prior Anti-VEGF Treatment

Eyes with prior anti-VEGF treatment had a longer duration of macular edema at baseline (mean=18 months) compared with those without prior anti-VEGF treatment (1 month; adjusted t-test p<0.0001, Table 4). The ability to grade presence of subretinal fluid by SD-OCT differed between these two groups, with 6% of eyes with prior anti-VEGF treatment having "cannot grade" while 27% of eyes with no prior anti-VEGF having "cannot grade" to grade (adjusted chi-squared p=0.0101, Table 5). Area of intraretinal and/or subretinal hemorrhage within the grid based on fundus photography is larger in eyes with no prior anti-VEGF (total area of blood > 50% of Early Treatment Diabetic Retinopathy Study grid = 26%) than in the prior anti-VEGF group (6%, adjusted chi-squared p = <0.0001, Table 5).

DISCUSSION

At present, there are no randomized, controlled clinical trial data comparing the safety and efficacy of different anti-VEGF agents for the treatment of decreased vision due to macular edema associated with retinal vein occlusion. SCORE2 was designed to determine if bevacizumab is non-inferior to aflibercept for the treatment of decreased vision due to macular edema secondary to CRVO, to investigate whether the frequency of intravitreal injections can be reduced in eyes that have responded well to anti-VEGF treatment, and to assess the impact of alternative treatment strategies (a different anti-VEGF agent or intravitreal dexamethasone) in eyes that have not responded well to an anti-VEGF agent.

To investigate the comparability of the SCORE2 population to those of prior clinical trials, we compared the baseline characteristics of the SCORE2 participants with baseline characteristics from other clinical studies that have evaluated patients with CRVO. The comparison described herein and summarized in Table 6 includes participants from the SCORE-CRVO trial,[17] CRUISE trial,[18] Copernicus trial,[19] Galileo Study,[20] CVOS (group M study),[7] Geneva trial,[31] CVOS (group M study),[7] and the Eye Disease Case-Control Study (EDCCS).[43] Across these studies, the mean patient age was in the 60s (range of the means: 62–69 years), the proportion of women participating ranged from 41% to 47%, the

mean baseline E-ETDRS visual acuity letter score was close to 50 (range: 48–54; letters were not reported for group M of the CVOS but the mean Snellen equivalent, 20/125, was comparable to that of the other studies), and the mean OCT-measured central subfield thickness ranged from 552–685 um. At baseline, the study population of the Geneva Study had the best mean visual acuity letter score (54) and the lowest OCT-measured central subfield thickness (552 um); this is likely because the Geneva Study included patients with BRVO as well as patients with CRVO.[31] The reported duration of disease is longer in SCORE2 compared to previous CRVO trials (Table 6), but since estimation of disease duration is generally based on patients' recollection of symptom duration, it is unknown whether the disease duration differs meaningfully among the CRVO trials.

In SCORE2, 77% of participants had a self-reported history of hypertension. In the SCORE-CRVO trial, Geneva Trial, and EDCCS, the proportion of patients with a history of hypertension was 73%, 63%, and 56%, respectively. In the CVOS, 57% of participants were reported to be taking medication for hypertension or had elevated blood pressure at baseline. In SCORE2, 31% of participants had a history of diabetes mellitus. In the SCORE-CRVO trial, Geneva Trial, CVOS and EDCCS, the proportion of patients with a history of diabetes mellitus was 23%, 15%, 7% and 9%, respectively. The literature supports that the incidence and prevalence of diabetes mellitus[44, 45] and hypertension[46, 47] have increased in the last few decades in the United States; the increasing prevalence of these two conditions in CRVO trials over time may be reflective of the increasing prevalence of these conditions in the general population over time.

The CRVO and HRVO patients enrolled into SCORE2 are similar in many respects. Demographic characteristics such as gender, ethnicity, age, history of coronary artery disease, hypertension and history of cancer were similar between both groups and were balanced within cohort with respect to the treatment groups. The racial disparity (38% of HRVO patients were black, while only 11% of CRVO patient were) echoes findings from the earlier SCORE Study, in which 17% of HRVO patients were black, while only 4% of CRVO patients were.[48] Coupled with the small adjusted p-value, the two studies provide very strong evidence that the association is real, although the causality remains obscure. At baseline, the area of intraretinal and/or subretinal hemorrhage within the grid based on fundus photography was significantly larger in CRVO than HRVO eyes; this makes sense given that the clinical distinction between CRVO and HRVO is made based on the area of retina affected by the RVO. There was high agreement (98%) between investigators and the SCORE2 Reading Center on the diagnosis of CRVO, and lower agreement (70%) on the diagnosis of HRVO. In 15 (28%) of the 54 eyes that the clinical site investigator determined had a HRVO, the Reading Center graded the retinal vein occlusion as a CRVO. We speculate that investigators determined presence of HRVO when there was a clear predominance of retinal hemorrhages in two retinal quadrants (superior or inferior) while the Reading Center graded CRVO if any biomarkers for retinal vein occlusion (such as dilated and tortuous veins or intraretinal hemorrhage) were present in each of the remaining two quadrants. In 1 (2%) eye identified as having a HRVO by the clinical site investigator, the Reading Center identified a branch retinal vein occlusion because the retinal hemorrhages occupied fewer than 2 quadrants of the retina.

Comparison of fundus photographs in study eyes with and without prior anti-VEGF treatment demonstrated a significantly larger area of intraretinal and/or subretinal hemorrhage within the grid in eyes with no prior anti-VEGF therapy. This is likely because eyes treated previously with anti-VEGF had a significantly longer duration of macular edema compared to eyes not treated previously with anti-VEGF, which would have permitted more time for intraretinal and/or subretinal hemorrhage to resolve in the former compared to the latter eyes. In addition, perhaps anti-VEGF therapy speeds up resolution of intraretinal/subretinal hemorrhage. The larger area of intraretinal and/or subretinal hemorrhage in the eyes without prior anti-VEGF therapy, in turn, likely explains the higher proportion of eyes in this group having “cannot grade” for the presence of subretinal fluid on SD-OCT since large areas of blood may block the visibility of subretinal fluid.

The SCORE2 cohort is a heterogeneous population, including both CRVO and HRVO eyes and both treatment-naive eyes and eyes treated previously with anti-VEGF, which will allow study results to have broad applicability to CRVO and HRVO patients receiving treatment for macular edema. Similarities of the baseline characteristics of the SCORE2 population to other CRVO trial cohorts will allow meaningful comparisons of outcome results across trials.

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Abbreviations

AMD	age-related macular degeneration
Anti-VEGF	anti-vascular endothelial growth factor
AREDS	Age-Related Eye Disease Study
CRVO	central retinal vein occlusion
DCC	Data Coordinating Center
DME	diabetic macular edema
EDCCS	1Eye Disease Case-Control Study
E-ETDRS	electronic visual acuity test
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FDA	Food and Drug Administration
HRVO	hemiretinal vein occlusion
IOP	intraocular pressure

IS-OS	inner segment-outer segment
NEI	National Eye Institute
NEI VFQ-25	National Eye Institute Visual Function Questionnaire-25
OCT-CST	optical coherence tomography-measured central subfield thickness
OCTTC	Ophthalmic Clinical Trial Training and Certification
PRN	pro re nata
SCORE	***S***tandard Care versus ***CO***rticosteroid for ***RE***tinal Vein Occlusion Study
SCORE2	***S***tudy of ***CO***mparative Treatments for ***RE***tinal Vein Occlusion 2
SD-OCT	spectral domain optical coherence tomography
TAE	treat and extend
VALS	visual acuity letter score

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SCORE2 Highlights

The SCORE2 cohort is a heterogeneous population of CRVO and HRVO eyes and includes a subset of eyes treated previously with anti-VEGF which will allow broad applicability of results to patients treated for macular edema.

Table 1

Listing of SCORE2 Secondary Outcomes

	Secondary Outcomes
Efficacy	Visual acuity • Proportion with improvement or worsening by 15 or more in visual acuity letter score • Proportion meeting E-ETDRS visual acuity letter score of 70 (approximate Snellen equivalent of 20/40) or better • Absolute and change from baseline to each month visit in visual acuity letter score and within subgroups of (1) baseline visual acuity strata; (2) history and no history of anti-VEGF treatment prior to baseline, and (3) CRVO and HRVO disease status Spectral domain optical coherence tomography • Absolute and change from baseline in central retinal thickness, center point thickness, and macular volume • Presence of intraretinal cystoid spaces and subretinal fluid • Photoreceptor length Color fundus photography • Area of retinal thickness and hemorrhage Ultra-widefield fluorescein angiography • Area of peripheral retinal nonperfusion (defined as the absence of retinal arterioles and/or capillaries and detected by characteristics such as a “pruned” appearance of adjacent arterioles and a darker appearance of the choroid) and area of fluorescein leakage National Eye Institute Visual Function Questionnaire-25 • Absolute and change from baseline in total score and subscale scores
Safety	Ocular events: • Increased IOP and surgery to lower IOP • Infectious and culture-negative endophthalmitis • Retinal detachment • Vitreous hemorrhage • New-onset retinal arterial occlusion • Neovascular events Systemic: • Arterial thromboembolic events as defined by the Antiplatelet Trialists’ Collaboration[1]

[1]Antiplatelet Trialists’ Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81–106.

Table 2

Study Eye Inclusion and Exclusion Criteria

Inclusion criteria • Best corrected electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) visual acuity letter 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 letter score between 19 and 33 is perfused. • Center-involved macular edema due to central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO) present on clinical examination. Note: Enrollment limited to no more that 25% of the planned sample size with HRVO eyes. • 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 must be 320 μm or greater. • Media clarity, pupillary dilation, and participant cooperation sufficient for adequate fundus photographs.
Exclusion criteria • 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. • Presence of an ocular condition such that visual acuity would not improve from resolution of the edema (e.g., foveal atrophy). • 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. • Substantial cataract estimated to have reduced visual acuity by 3 lines or more. • History of laser photocoagulation for macular edema within 3 months prior to randomization. • History of intravitreal corticosteroid within 4 months of randomization. • Intravitreal anti-VEGF injection within 2 months of randomization. Note: Enrollment limited to no more than 25% of the planned sample size with any history of anti-VEGF treatment. • History of peribulbar or retrobulbar corticosteroid use for any reason within 2 months prior to randomization. • 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. • 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. • History of YAG capsulotomy performed within 2 months prior to randomization. • Aphakia. • Presence of an anterior chamber intraocular lens. • Examination evidence of external ocular infection, including conjunctivitis, chalazion or significant blepharitis. • History of macular detachment. • Examination evidence of any diabetic retinopathy.

Table 3

Measurement and Examination Procedures for Scheduled Study Evaluations

Visit	Medical	E-ETDRS Refraction	E-ETDRS Visual Acuity	SD- OCT	IOP	Ophthalmic exam*	Lens Exam	Fundus Photos**	NEI VFQ-25	Treatment***	Ultra- widefield FA****
Screening/randomization	X	X	X	X	X	X	X	X	X	Bev or Afl	X
Primary Outcome Period											
At Months 1, 2, 3, 4, and			X	X	X	X				Bev or Afl	
At Month 6		X	X	X	X	X	X	X	X	Bev or Afl or Dex	X
Secondary Outcome Period											
Good Responders											
Months 7, 8, 9, 10, and 11, or TAE			X	X	X	X				Bev or Afl	
Poor or Marginal Responders in Afl arm											
Month 6, PRN at Month 9, 10, or 11			X	X	X	X				Dex	
Poor or Marginal Responders in Bev arm											
Months 6, 7, 8 and TAE			X	X	X	X				Afl	
At Month 12		X	X	X	X	X	X	X	X		X

E-ETDRS = electronic Early Treatment Diabetic Retinopathy Study. SD-OCT = Spectral Domain optical coherence tomography. IOP = intraocular pressure. FA = Fluorescein angiogram. TAE=Treat and Extend. Bev=bevacizumab. Afl=aflibercept. Dex=Dexamethasone.

* Includes both a dilated fundus examination and a slit-lamp examination.

** Modified 3-Field photos on study eye only.

*** Injection treatment between Months 1 and 5 is Bev or Afl, depending on initial randomization assignment. Good responders continue Bev or Afl on monthly or TAE schedule between Months 7 and 11 according to secondary randomization. Dex provided at Month 6 and PRN at Month 9, 10 or Month 11 in Poor or Marginal Responders initially randomized to Afl. Afl provided at Months 6, 7, 8 and TAE in Poor or Marginal Responders initially randomized to Bev.

**** Ultra-widefield FA performed at a subgroup of sites that have this ability.

Table 4

Baseline Characteristics of SCORE2 Participants[1]

	Randomized Treatment Assignment		Disease Type		Anti-VEGF Treatment Prior to SCORE2		Total
Characteristic[2]	**Aflibercept**	**Bevacizumab**	**CRVO**	**HRVO**	**No**	**Yes**	
Number of participants	**180**	**182**	**307**	**55**	**241**	**121**	**362**
Demographic Characteristics							
Age (years) – mean (SD)	69(11)	69(13)	69(12)	70(13)	68(12)	71(11)	69(12)
< 50 (%)	7(3.9)	15(8.2)	18(5.9)	4(7.3)	18(7.5)	4(3.3)	22(6.1)
50-<60 (%)	28(15.6)	26(14.3)	48(15.6)	6(10.9)	38(15.8)	16(13.2)	54(14.9)
60-<70 (%)	59(32.8)	48(26.4)	95(30.9)	12(21.8)	74(30.7)	33(27.3)	107(29.6)
70-<80 (%)	58(32.2)	52(28.6)	92(30.0)	18(32.7)	65(27.0)	45(37.2)	110(30.4)
≥ 80 (%)	28(15.6)	41(22.5)	54(17.6)	15(27.3)	46(19.1)	23(19.0)	69(19.1)
Women (%)	82(45.6)	75(41.2)	136(44.3)	21(38.2)	96(39.8)	61(50.4)	157(43.4)
White (%)	131(72.8)	145(79.7)	246(80.1)	30(54.5)	186(77.2)	90(74.4)	276(76.2)
Black (%)	28(15.6)	26(14.3)	33(10.7)	21(38.2)	35(14.5)	19(15.7)	54(14.9)
Other (%)	21(11.7)	11(6.0)	28(9.1)	4(7.3)	20(8.3)	12(9.9)	32(8.8)
Not Hispanic or Latino (%)	164(91.1)	160(87.9)	274(89.3)	50(90.9)	214(88.8)	110(90.9)	324(89.5)
Study Eye Characteristics							
E-ETDRS visual acuity letter score – mean (SD)	50(15)	50(15)	50(15)	54(14)	50(15)	50(15)	50(15)
59–73 (20/40 to 20/63) (%)	66(36.7)	67(36.8)	108(35.2)	25(45.5)	88(36.5)	45(37.2)	133(36.7)
49–58 (20/80 to 20/100) (%)	43(23.9)	42(23.1)	70(22.8)	15(27.3)	58(24.1)	27(22.3)	85(23.5)
19–48 (20/125 to 20/400) (%)	71(39.4)	73(40.1)	129(42.0)	15(27.3)	95(39.4)	49(40.5)	144(39.8)
Duration of macular edema (months) – mean (SD)	8(17)	5(10)	7(14)	3(10)	1(3)	18(19)	6(14)
Missing	1(0.6)	1(0.5)	2(0.7)	0(0.0)	0(0.0)	2(1.7)	2(0.6)
<3 (%)	114(63.3)	129(70.9)	199(64.8)	44(80.0)	230(95.4)	13(10.7)	243(67.1)
3 – 6 (%)	18(10.0)	11(6.0)	25(8.1)	4(7.3)	8(3.3)	21(17.4)	29(8.0)
7 – 12 (%)	17(9.4)	17(9.3)	30(9.8)	4(7.3)	2(0.8)	32(26.4)	34(9.4)
>12 (%)	30(16.7)	24(13.2)	51(16.6)	3(5.5)	1(0.4)	53(43.8)	54(14.9)
OCT central subfield (microns) – mean (SD)	665(220)	690(238)	691(230)	606(213)	689(229)	655(231)	678(230)

	Randomized Treatment Assignment		Disease Type		Anti-VEGF Treatment Prior to SCORE2		Total
Characteristic[2]	**Aflibercept**	**Bevacizumab**	**CRVO**	**HRVO**	**No**	**Yes**	
Prior anti-VEGF treatment	65(36.1)	56(30.8)	108(35.2)	13(23.6)	-	121(100)	121(33.4)
HRVO	24(13.3)	31(17.0)	-	55(100)	42(17.4)	13(10.7)	55(15.2)
Lens Status							
Cataract extraction	43(23.9)	55(30.2)	83(27.0)	15(27.3)	57(23.7)	41(33.9)	98(27.1)
Natural lens, history of cataract	108(60.0)	95(52.2)	170(55.4)	33(60.0)	137(56.8)	66(54.5)	203(56.1)
Natural lens, no history of cataract	29(16.1)	32(17.6)	54(17.6)	7(12.7)	47(19.5)	14(11.6)	61(16.9)
Other Clinical Characteristics							
Diabetes mellitus (%)							
Type 1	1(0.6)	0(0.0)	1(0.3)	0(0.0)	0(0.0)	1(0.8)	1(0.3)
Type 2	54(30.0)	59(32.4)	95(30.9)	18(32.7)	74(30.7)	39(32.2)	113(31.2)
Hypertensive (%)	140(77.8)	138(75.8)	236(76.9)	42(76.4)	184(76.3)	94(77.7)	278(76.8)
Coronary artery disease (%)	26(14.4)	29(15.9)	48(15.6)	7(12.7)	34(14.1)	21(17.4)	55(15.2)
NEI-VFQ-25 overall score	77(15)	77(17)	77(16)	78(16)	76(16)	78(16)	77(16)

[1] P-values that are less than 0.05, either before adjustment (comparing treatment groups), or after adjustment (comparing CRVO vs HRVO, or prior versus no prior anti VEGF) are highlighted

[2] Mean (Std Dev) unless otherwise noted

Table 5

Baseline Image Characteristics of the Study Eye of SCORE2 Participants[1]

	Randomized Treatment Assignment		Disease Type		Anti-VEGF Treatment Prior to SCORE2		Total
Characteristic[2]	**Aflibercept**	**Bevacizumab**	**CRVO**	**HRVO**	**No**	**Yes**	
			OCT				
Number of images evaluated for Center Point	156	164	270	50	218	102	320
Retinal thickness: Center Point - mean (SD)	0.69(0.24)	0.71(0.26)	0.71(0.25)	0.61(0.24)	0.71(0.25)	0.67(0.25)	0.70(0.25)
Number of images evaluated for Total Volume	43	42	72	13	47	38	85
Retinal thickness: Total Volume – mean (SD)	9.95(2.73)	10.1(1.62)	10.0(2.25)	9.77(2.28)	10.2(2.67)	9.75(1.56)	10.0(2.24)
Number of images assessed	162	167	277	52	223	106	329
Presence of subretinal fluid							
Absent	41(25.3)	31(18.6)	61(22.0)	11(21.2)	42(18.8)	30(28.3)	72(21.9)
Questionable	6(3.7)	13(7.8)	16(5.8)	3(5.8)	12(5.4)	7(6.6)	19(5.8)
Definite, central subfield involved	86(53.1)	86(51.5)	139(50.2)	33(63.5)	110(49.3)	62(58.5)	172(52.3)
Definite, outside central subfield	1(0.6)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	1(0.9)	1(0.3)
Cannot grade	28(17.3)	37(22.2)	60(21.7)	5(9.6)	59(26.5)	6(5.7)	65(19.8)
Cystoid spaces							
Absent	0(0.0)	1(0.6)	0(0.0)	1(1.9)	1(0.4)	0(0.0)	1(0.3)
Questionable	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Definite, central subfield involved	158(97.5)	165(98.8)	272(98.2)	51(98.1)	219(98.2)	104(98.1)	323(98.2)
Definite, outside central subfield	2(1.2)	1(0.6)	3(1.1)	0(0.0)	1(0.4)	2(1.9)	3(0.9)
Not applicable	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Intraretinal fluid							
Absent	0(0.0)	1(0.6)	0(0.0)	1(1.9)	1(0.4)	0(0.0)	1(0.3)
Questionable	0(0.0)	1(0.6)	1(0.4)	0(0.0)	0(0.0)	1(0.9)	1(0.3)
Definite, central subfield involved	160(98.8)	165(98.8)	274(98.9)	51(98.1)	220(98.7)	105(99.1)	325(98.8)
Definite, outside central subfield	2(1.2)	0(0.0)	2(0.7)	0(0.0)	2(0.9)	0(0.0)	2(0.6)

	Randomized Treatment Assignment		Disease Type		Anti-VEGF Treatment Prior to SCORE2		Total
Characteristic[2]	**Aflibercept**	**Bevacizumab**	**CRVO**	**HRVO**	**No**	**Yes**	
Posterior vitreous detachment							
Absent	83(51.2)	90(53.9)	147(53.1)	26(50.0)	106(47.5)	67(63.2)	173(52.6)
Questionable	10(6.2)	7(4.2)	13(4.7)	4(7.7)	13(5.8)	4(3.8)	17(5.2)
Definite, non-adherent	4(2.5)	5(3.0)	7(2.5)	2(3.8)	6(2.7)	3(2.8)	9(2.7)
Definite, questionable adherent	6(3.7)	7(4.2)	12(4.3)	1(1.9)	10(4.5)	3(2.8)	13(4.0)
Definite, partially adherent	58(35.8)	56(33.5)	96(34.7)	18(34.6)	85(38.1)	29(27.4)	114(34.7)
Not applicable	1(0.6)	2(1.2)	2(0.7)	1(1.9)	3(1.3)	0(0.0)	3(0.9)
Epiretinal membrane							
Absent	55(34.0)	57(34.1)	91(32.9)	21(40.4)	83(37.2)	29(27.4)	112(34.0)
Questionable	35(21.6)	44(26.3)	65(23.5)	14(26.9)	61(27.4)	18(17.0)	79(24.0)
Definite, central subfield involved	9(5.6)	11(6.6)	19(6.9)	1(1.9)	10(4.5)	10(9.4)	20(6.1)
Definite, outside central subfield	62(38.3)	54(32.3)	101(36.5)	15(28.8)	67(30.0)	49(46.2)	116(35.3)
Not applicable	1(0.6)	1(0.6)	1(0.4)	1(1.9)	2(0.9)	0(0.0)	2(0.6)
Retinal traction and distortion							
Absent	59(36.4)	61(36.5)	97(35.0)	23(44.2)	89(39.9)	31(29.2)	120(36.5)
Questionable	30(18.5)	42(25.1)	60(21.7)	12(23.1)	56(25.1)	16(15.1)	72(21.9)
Definite, central subfield involved	9(5.6)	11(6.6)	19(6.9)	1(1.9)	10(4.5)	10(9.4)	20(6.1)
Definite, outside central subfield	63(38.9)	52(31.1)	100(36.1)	15(28.8)	66(29.6)	49(46.2)	115(35.0)
Not applicable	1(0.6)	1(0.6)	1(0.4)	1(1.9)	2(0.9)	0(0.0)	2(0.6)
Macular hole							
Absent	158(97.5)	165(98.8)	274(98.9)	49(94.2)	220(98.7)	103(97.2)	323(98.2)
Questionable	1(0.6)	1(0.6)	0(0.0)	2(3.8)	2(0.9)	0(0.0)	2(0.6)
Pseudohole or lamellar hole	2(1.2)	0(0.0)	2(0.7)	0(0.0)	0(0.0)	2(1.9)	2(0.6)
Cannot grade	1(0.6)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	1(0.9)	1(0.3)
Not applicable	0(0.0)	1(0.6)	0(0.0)	1(1.9)	1(0.4)	0(0.0)	1(0.3)
Status of IS-OS within central subfield							
Normal	2(1.2)	1(0.6)	3(1.1)	0(0.0)	2(0.9)	1(0.9)	3(0.9)

	Randomized Treatment Assignment		Disease Type		Anti-VEGF Treatment Prior to SCORE2		Total
Characteristic[2]	**Aflibercept**	**Bevacizumab**	**CRVO**	**HRVO**	**No**	**Yes**	
Questionably abnormal	7(4.3)	7(4.2)	14(5.1)	0(0.0)	5(2.2)	9(8.5)	14(4.3)
Definitely abnormal, absent	14(8.6)	14(8.4)	23(8.3)	5(9.6)	19(8.5)	9(8.5)	28(8.5)
Definitely abnormal, patchy	22(13.6)	16(9.6)	28(10.1)	10(19.2)	24(10.8)	14(13.2)	38(11.6)
Cannot grade	117(72.2)	128(76.6)	208(75.1)	37(71.2)	172(77.1)	73(68.9)	245(74.5)
Not applicable	0(0.0)	1(0.6)	1(0.4)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Color Fundus Photograph							
Number of images evaluated	173	176	295	54	233	116)	349
Type of vein occlusion							
Central	152(87.9)	152(86.4)	289(98.0)	15(27.8)	193(82.8)	111(95.7)	304(87.1)
Hemicentral	20(11.6)	23(13.1)	5(1.7)	38(70.4)	39(16.7)	4(3.4)	43(12.3)
Branch	0(0.0)	1(0.6)	0(0.0)	1(1.9)	1(0.4)	0(0.0)	1(0.3)
Cannot Grade	1(0.6)	0(0.0)	1(0.3)	0(0.0)	0(0.0)	1(0.9)	1(0.3)
Area of intraretinal and/or subretinal hemorrhage within grid							
Total area of blood 1 to < 25% of grid	92(53.2)	83(47.2)	153(51.9)	22(40.7)	90(38.6)	85(73.3)	175(50.1)
Total area of blood 25 to 50% of grid	49(28.3)	45(25.6)	67(22.7)	27(50.0)	82(35.2)	12(10.3)	94(26.9)
Total area of blood >50% of grid	25(14.5)	42(23.9)	63(21.4)	4(7.4)	60(25.8)	7(6.0)	67(19.2)
Cannot Grade	0(0.0)	1(0.6)	1(0.3)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Not applicable	7(4.0)	5(2.8)	11(3.7)	1(1.9)	0(0.0)	12(10.3)	12(3.4)

[1] P-values that are less than 0.05, either before adjustment (comparing treatment groups), or after adjustment (comparing CRVO vs HRVO, or prior versus no prior anti VEGF) are highlighted

[2] Mean (Std Dev) unless otherwise noted

Table 6

Comparison of SCORE2 Baseline Characteristics to other Studies in CRVO

	Clinical Trial							
	SCORE2 (includes 55 HRVO eyes)	**SCORE- CRVO**	**CRUISE**	**Copernicus**	**Galileo**	**Geneva (includes 830 BRVO)**	**CVOS Group M**	**EDCCS** ** **(non-ischemic eyes)**
Sample size	362	271	392	187	177	1267	155	148
Age (mean)	69	68	68	66	62	64	67	NR
Women (%)	43%	45%	43%	43%	44%	47%	41%	48%
White (%)	76%	91%	84%	79%	72%	75%	94%	76%
Black (%)	15%	4%	9%	5%	0%	4%	NR	NR
E-ETDRS visual acuity letter score (mean)	50 (~20/100)	51 (~20/100)	48 (~20/125)	50 (~20/100)	52 (~20/100)	54 (~20/80)	(letters NR) 20/125	NR
OCT central subfield in microns (mean)	678	600 *	685	666	666	552	NR	NR
Duration of disease before enrollment (months)	6	4	3	2	3	5	NR (0% < 1 month)	NR
Hypertension	77%	73%	NR	NR	NR	63%	57%	56%
Diabetes mellitus	32%	23%	NR	NR	NR	15%	7%	9% ***
Coronary heart disease	15%	21%	NR	NR	NR	11%	NR	17%
NEI-VFQ-25 overall score	77	NR	NR	78	NR	NR	NR	NR

* based on 1st Screening OCT

** The EDCCS publication[44] provided findings separately for ischemic and non-ischemic eyes, and participants with non-ischemic eyes were chosen as the comparison group. For comparison, of participants with ischemic CRVO, 79% had hypertension and 17% were taking insulin or hypoglycemics.

*** taking insulin or hypoglycemics

NR=not reported in literature