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SCORE Study Report 3: Study Design and Baseline Characteristics

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Abstract

Objective—To describe the baseline characteristics of the participants in the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) Study and to compare with cohorts from other retinal vein occlusion trials. The design of the SCORE Study is also described.

Design—Two multicenter phase 3 randomized clinical trials, one involving participants with central retinal vein occlusion (CRVO) and one involving participants with branch retinal vein occlusion (BRVO).

Participants—682 participants, including 271 with CRVO and 411 with BRVO.

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

Main outcome measures—Baseline ophthalmic characteristics, including visual acuity and duration of macular edema prior to enrollment, and medical history characteristics, including diabetes mellitus and hypertension.

Results—In the CRVO trial, at baseline, mean visual acuity letter score was 51 (~20/100), mean optical coherence tomography (OCT)-measured central subfield thickness was 595 microns, mean area of retinal thickening in the macular grid on color photography was 12.3 disc areas and mean area of fluorescein leakage was 11.0 disc areas. In the BRVO trial, at baseline, mean visual acuity letter score was 57 (~20/80), mean OCT-measured central subfield thickness was 491 microns, mean area of retinal thickening in the macular grid on color photography was 7.5 disc areas and the mean area of fluorescein leakage was 6.1 disc areas.

Conclusions—Differences observed in baseline visual acuity, OCT-measured retinal thickness, area of retinal thickening on color photography and area of fluorescein leakage support the evaluation of CRVO and BRVO in separate trials.

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This article contains online-only material. The following should appear online-only: Table 4.

Introduction

Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are common retinal vascular diseases, with concomitant macular edema reported to be a frequent cause of vision loss.¹⁻⁴ Current treatment modalities for macular edema are often unsatisfactory. At present, no treatment has been proven effective for macular edema from CRVO.^{5,6,7} Grid laser photocoagulation is effective for macular edema from BRVO, but many patients derive only limited benefit from it.¹ Several other treatment modalities have been evaluated for retinal vein occlusion; none has yet been conclusively proven to be safe or effective.⁸⁻¹⁸ The identification of additional treatments that are safe and effective is desirable and of public health importance.

The Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) Study, sponsored by the National Institutes of Health, National Eye Institute (NEI), consists of two multicenter, randomized, phase 3 clinical trials comparing the efficacy and safety of standard care with intravitreal injection(s) of triamcinolone acetonide (hereafter referred to as intravitreal triamcinolone) in either a 1 mg or a 4 mg dose for vision loss associated with macular edema secondary to CRVO and BRVO.¹⁹

The purpose of this report is to describe the study objectives and protocol. Demographic, systemic, and ocular characteristics of the subject population at study entry are also described. The baseline characteristics of the CRVO participants are compared with the baseline characteristics of the BRVO participants. Additionally, the SCORE Study cohort is compared with cohorts from other studies that have evaluated patient populations with CRVO and BRVO.^{1,2,5,20,21,22,23}

Study Design and Methods

Study Synopsis

The SCORE Study consists of two phase 3, multi-center, randomized clinical trials: one for CRVO and one for BRVO. The primary objective of the SCORE Study is to compare, within each trial, visual acuity outcome at one year among 3 groups of participants with vision loss associated with macular edema secondary to CRVO and BRVO. Participants were randomly assigned to receive standard care, 1 mg intravitreal triamcinolone or 4 mg intravitreal triamcinolone. Secondary objectives include comparing changes in retinal thickness as assessed by stereoscopic color fundus photography and optical coherence tomography (OCT). Safety objectives include estimating the incidence of infectious endophthalmitis, non-infectious endophthalmitis, retinal detachment, vitreous hemorrhage, cataract and elevated intraocular pressure (IOP). Study participants will be followed for 1 to 3 years after randomization. An abbreviated description of the SCORE Study design and methods is given herein; a full description is provided elsewhere.^{24,25}

Participating study personnel such as physician investigators and study coordinators were certified by the Data Coordinating Center (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 the Data Coordinating Center and photographers and technicians who performed the fundus photographs, OCT images and fluorescein angiograms for this study were certified by the University of Wisconsin Fundus Photograph Reading Center (Reading Center) before personnel could participate in this study.

The SCORE Study protocol and informed consent were approved by the respective clinical center institutional review boards or a centralized institutional review board. Investigators at 84 clinical centers randomized and followed SCORE Study participants in accordance with

the study protocol and Manual of Procedures. Men and women at least 18 years of age could each contribute at most one study eye. Table 1 reports the major ocular inclusion and exclusion criteria.

Screening and Randomization

Prospective participants were first consented for screening, and 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; (2) ophthalmic examination including dilated ophthalmoscopy and slit lamp examination (for lens assessment, modified Age-Related Eye Disease Study [AREDS] grading was used²⁶); (3) color fundus photographs, fluorescein angiography (FA), and optical coherence tomography (OCT), with the mean of two OCT measurements (central subfield thickness) used to assess eligibility (OCT 2 or OCT 3 [Carl Zeiss Meditec; Dublin, CA]); (4) blood pressure measurement; (5) for women of childbearing potential, a urine pregnancy test. Within 8 days of randomization, measurement of visual acuity and manifest refraction were required, using the electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) visual acuity method at 3 meters by a SCORE Study certified technician. All imaging tests (color fundus photographs, FA and OCT) were sent to the Reading Center.

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 Data Coordinating Center, to one of three equally-sized parallel arms in either the CRVO trial or the BRVO trial; the specific trial chosen for each participant was determined by the investigator following a protocol defined description of CRVO and BRVO. For the purposes of the SCORE Study, participants identified as having hemiretinal vein occlusion (HRVO) according to the definition outlined in the protocol were included in the BRVO trial. The arms for each of the two trials were: standard of care (SC), 1 mg intravitreal triamcinolone, and 4 mg intravitreal triamcinolone. Participants in the CRVO trial assigned to standard of care were observed. Participants in the BRVO trial assigned to standard care were treated with grid laser photocoagulation if a dense macular hemorrhage did not preclude treatment. If a dense hemorrhage was present, laser photocoagulation was postponed until clearing of the hemorrhage permitted laser treatment. In each trial, randomization was stratified by baseline visual acuity letter score: 73-59 (20/40 to 20/63); 58-49 (20/80 to 20/100); and 48-19 (20/125-20/400). BRVO participants were also stratified by presence or absence of baseline dense macular hemorrhage as determined by the investigator. The random sequence of treatment assignments was constructed before trial onset, using a separate permuted block design with random block sizes of (3, 6) within each stratum.

Participant visit schedule

Once randomized, all participants were expected to be followed for 1 to 3 years. Actual length of follow-up depended on the randomization date relative to the common close out date of February 28, 2009. Study visits were scheduled every 4 months following randomization (see Table 2). All participants who received intravitreal triamcinolone had additional safety visits, at which E-ETDRS testing, IOP and an eye examination were recorded, at 4 days (+/- 3 days) and at 4 weeks (+/- 1 week) following each injection. At all other study visits, participants had E-ETDRS testing, IOP measurement, an eye examination and an OCT scan. OCT scans were performed in both eyes at baseline, 4 months and at the annual visits. At the other 4-month interval visits, an OCT scan was performed only for the study eye. Stereoscopic color fundus photographs (7 fields) were taken of the study eye at baseline and at the annual visits. Three-field photographs of the study eye were taken at the 4, 8, 16, 20, 28, and 32 month visits. Three-field photographs of the non-study eye were taken at baseline and at the annual visits.

Fluorescein angiography was performed at baseline, 4 months and at the annual visits. Blood pressure measurement was taken at baseline and was repeated at the annual visits.

Follow up and retreatment guidelines

Participants were retreated with the randomly assigned treatment at 4-month intervals except when the criteria to defer additional treatment or to employ the alternate treatment regimen were satisfied. However, even if these criteria were met, the subject could still be re-treated with the assigned treatment at the discretion of the investigator.

Retreatment criteria—The three reasons to consider deferral of re-treatment were: (1) treatment had been successful (either the investigator believed that the macula was flat with an OCT central subfield thickness of ≤ 225 microns, the visual acuity score was 79 or more letters [20/25 or better], or there was substantial improvement in macular edema from the last treatment session [e.g., $\geq 50\%$ decrease in retinal thickness on the OCT central subfield]); (2) treatment was contraindicated because either the subject had a significant adverse effect from prior treatment or maximum treatment had already been received (e.g. there was a prior IOP rise that required treatment or maximal laser treatment had already been performed in an eye with BRVO); or (3) additional treatment was considered “apparently futile”. Treatment was “apparently futile” if a period of 8 or more months transpired during which there were 2 procedures (either two laser photocoagulation sessions or two intravitreal triamcinolone injections were performed, according to the randomization assigned treatment) and during which there was no evidence of at least borderline improvement. Borderline improvement was deemed present if, compared with findings at the beginning of the 8 or more month period, there was an increase in visual acuity score of 5 or more letters. Borderline improvement was also deemed present if there was a decrease in calculated OCT-measured retinal thickening (actual central subfield thickness minus mean normal retinal thickness in the central subfield) that was at least 50 microns and represented at least a 20% reduction in retinal thickening compared with the findings at the beginning of the 8 or more month period.

Alternate treatment criteria—Study eyes could receive the alternate treatment modality when there was a 15-letter or more decrease from baseline in best-corrected visual acuity that was present at two consecutive 4-month interval visits. The decrease in visual acuity had to be a result of persistent or recurrent macular edema (i.e., not due to cataract or other abnormality) that was documented on OCT.

If the alternate treatment criteria were met, eyes assigned to the laser group could receive (but were not required to receive) triamcinolone (4mg dose, study formulation), and eyes assigned to one of the triamcinolone groups (BRVO eyes only) could receive (but were not required to receive) grid laser photocoagulation.

Additional detailed criteria for re-treatment and application of the alternate treatment regimen are available elsewhere.^{24,25}

Treatment protocol

Intravitreal Injection—All study eyes assigned to triamcinolone received a standardized ocular surface preparation procedure prior to the injection. This preparation procedure consisted of: (1) administration of topical gatifloxacin on the day of injection (use of 3 drops over a period of at least 15 minutes); (2) application of a topical anesthetic followed by holding a cotton-tipped applicator soaked in topical anesthetic over the injection site, or application of lidocaine gel, or use of a subconjunctival anesthetic; (3) asepsis 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); and (4) use of a sterile eyelid speculum to separate the eyelids.

The study drug was formulated and manufactured as a sterile, preservative-free, micronized triamcinolone acetonide injectable suspension (4mg brand name TRIVARIS™, Allergan, Inc, Irvine, CA) of 1mg or 4mg per 0.05cc. Following the preparation procedure, either 1 mg or 4 mg of triamcinolone 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 triamcinolone and to confirm that the central retinal artery was perfused. Subjects were instructed to use topical gatifloxacin 4 times daily for 3 days following the injection.

Grid Laser Photocoagulation—The grid laser photocoagulation treatment technique used in the BRVO trial was similar to that performed in the BVOS and is the treatment approach that is used commonly in clinical practice.¹ This technique was used for both the initial treatment and for any re-treatment that was performed. The general grid laser photocoagulation parameters were: (1) treatment between 500 and 3000 microns from the center of the macula; (2) green to yellow wavelength; (3) spot size of 50-100 microns; (4) burn duration of 0.05 to 0.1 seconds; (5) grid treatment applied to areas of diffuse retinal thickening and focal leaks, if present; (6) barely visible to light gray burn intensity; (7) burn separation of 1-2 visible burns widths apart.

Statistical methods

The primary efficacy outcome is a gain from baseline in study eye best-corrected E-ETDRS visual acuity letter score of 15 or more at the 12-month visit.

Outcomes are considered separately for each trial (CRVO, BRVO), with all three pairwise comparisons (standard care versus 1 mg, standard care versus 4 mg, 1 mg versus 4 mg) made within each trial. The three pairwise comparisons are made by means of logistic regression adjusting for baseline visual acuity, clinical site, and presence of baseline macular hemorrhage in participants with BRVO. Family-wide error (FWE) is controlled separately within each trial at $\alpha = 0.05$ by a closed test method.²⁷ Interim monitoring is implemented through an alpha-spending approach with an initially-parsimonious spending function.

Participants within pre-specified, protocol defined windows will be analyzed. Participants without data in the pre-specified, protocol defined window will not be included in the primary analysis. Secondary efficacy analyses will explore analysis methods that impute for missing data and a sensitivity analysis will be performed in which outcomes will be assigned to missing eyes so as to explore both the minimum and maximum possible estimates of treatment effects. These additional analyses will explore the consistency of the results and provide more information as to the benefit or lack of benefit of the treatment.

To control FWE in the multiple-testing setting in Tables 3 and 4 (available at <http://aaojournal.org>), we provide p-values only for comparisons significant at $\alpha \leq 0.05$ after adjustment by Hochberg's sequentially-rejective method.²⁸ For each Hochberg-significant comparison, we present both the unadjusted p-value, denoted as p, and the Hochberg-adjusted p-value, denoted as p*.

Results

Between November 4, 2004 and February 29, 2008, 682 subjects were enrolled into the SCORE Study: 271 in the CRVO trial, and 411 in the BRVO trial. During the enrollment period, 461 clinical investigators, 318 clinical coordinators, 603 photographers/OCT technicians and 832 refractionists participated (a single individual could participate in multiple roles).

Baseline characteristics of study participants, both across trials and across treatment arms within trials, are displayed in Tables 3 and 4 (available at <http://aaojournal.org>). Table 3 summarizes demographic, ophthalmic, and other clinical data collected from participating clinical sites. Table 4 (available at <http://aaojournal.org>) presents color photograph, OCT and FA data analyzed at the Reading Center. When contrasting disease areas with respect to a particular variable, we provide the (CRVO, BRVO) values in parentheses.

Baseline description

Demographic and Study Eye Characteristics—The “Demographic Characteristics” panel of Table 3 shows that the mean age of participants in the SCORE Study was 67 years, 88% of participants were white and 91% non-Hispanic. There was a slight and non-significant preponderance of males (55%, 51%) in both trials.

The “Study Eye Characteristics” panel of Table 3 shows that the visual acuity letter score of CRVO participants was significantly worse than that of BRVO participants (51 [20/100] versus 57 [20/80]; $p < 0.0001$, $p^* < 0.0001$). CRVO and BRVO participants had macular edema for (4.3, 4.4) months before randomization. Twenty-nine percent of BRVO participants had dense macular hemorrhage at randomization and, if assigned to standard care, had laser treatment postponed until the hemorrhage cleared. CRVO participants were not assessed for dense macular hemorrhage at baseline. OCT-measured central subfield thickness in CRVO participants was significantly higher than that of BRVO participants (595 versus 491 microns; $p < 0.0001$, $p^* < 0.0001$). Fewer CRVO participants than BRVO participants had prior grid photocoagulation (0% versus 7%, $p < 0.0001$, $p^* = 0.0021$). There was no significant difference between the groups with respect to prior sector/panretinal photocoagulation (1%, 1%), intraocular pressure (15.5, 15.1 mm Hg), percent phakic eyes (81%, 81%), or (among phakic eyes) presence of nuclear (85%, 81%), cortical (32%, 24%), or posterior subcapsular opacities (9%, 11%). In the BRVO trial, a lower proportion of participants in the standard care group (13%) compared to the triamcinolone groups (28% and 32%) had cortical opacities ($p = 0.0025$, $p^* = 0.22$), a fact which we attribute to type I error. No other differences between arms are Hochberg-significant in Table 3.

The “Other Clinical Characteristics” panel of Table 3 shows that CRVO participants, compared with BRVO participants, more frequently reported a history of diabetes mellitus (22%, 14%). However, CRVO participants and BRVO participants did not differ significantly with respect to a history of hypertension (71%, 70%), coronary artery disease (20%, 18%), or cancer (21%, 17%).

Reading Center Assessment of Ophthalmic Images—The ETDRS macular grid was used to measure ophthalmic characteristics in the color photographs. The ETDRS macular grid consists of a circle 2 disc diameters (DD) in radius centered on the fovea (the grid), and an inner zone of 1 DD radius and a central subfield of 1/3 DD radius. The “Color Photographs” panel of Table 4 (available at <http://aaojournal.org>) shows that the area of retinal thickening was significantly greater in the CRVO group, both for the inner zone (3.7 v 2.6 disc areas, $p < 0.0001$, $p^* < 0.0001$) and the grid (12.3 v 7.5 disc areas, $p < 0.0001$, $p^* < 0.0001$). The two disease areas were similar with respect to the area of retinal hemorrhage in the inner zone, but

CRVO participants tended to have a larger area of retinal hemorrhage in the grid compared with BRVO participants (3.4 v 2.9 disc areas).

The second panel of Table 4 (available at <http://aaojournal.org>) summarizes baseline OCT measurements from the Reading Center. As with the OCT-measured central subfield measurements presented in Table 3, the center point measurements recorded by the Reading Center showed significantly greater values in the CRVO participants than in the BRVO participants (656 versus 525 microns $p < 0.0001$, $p^* < 0.0001$). The Reading Center used center point thickness for analysis since this permitted for correction of errors in the measurement of the inner and outer retinal boundaries. The CRVO and BRVO groups also differ with respect to the proportion of eyes with large cystoid spaces at the center point (35% v 17%, $p < 0.0001$, $p^* < 0.0001$), but were similar as to presence of definite vitreoretinal interface abnormalities (15%, 12%).

The “Fluorescein Angiogram” panel of Table 4 (available at <http://aaojournal.org>) shows that CRVO study eyes had significantly greater disc areas (DA) of fluorescein leakage in the inner zone (3.6 v 2.0 DA, $p < 0.0001$, $p^* < 0.0001$) and the grid (11.0 v 6.1 DA, $p < 0.0001$, $p^* < 0.0001$) compared with BRVO study eyes. However, CRVO study eyes had significantly smaller areas of capillary loss in the grid (0.2 v 0.6 DA, $p < 0.0001$, $p^* = 0.0015$) and significantly fewer eyes with > 5 DA of capillary loss (2% v 10%, $p < 0.0001$, $p^* = 0.0007$).

Discussion

At present, there are no randomized, controlled clinical trial data describing the efficacy and safety of intravitreal triamcinolone for macular edema associated with retinal vein occlusion.^{29,30} The SCORE Study was initiated to provide data from a randomized, controlled clinical trial regarding this treatment for vision loss associated with macular edema secondary to retinal vein occlusion. The SCORE Study consists of a CRVO clinical trial and a BRVO clinical trial.

The two cohorts enrolled into the SCORE Study are similar in many respects. Demographic characteristics such as gender, race, ethnicity, age, history of coronary artery disease, hypertension and history of cancer were similar between both cohorts and were balanced within cohort with respect to the 3 treatment groups. The main difference was the (non-significant) higher frequency of a history of diabetes mellitus in participants in the SCORE CRVO trial compared with participants in the SCORE BRVO trial. This is consistent with other clinical trials that have evaluated retinal vein occlusion.^{1,5,22,23}

Ophthalmic characteristics were similar at baseline for both cohorts with respect to intraocular pressure, lens status, duration of macular edema and history of prior sector or panretinal photocoagulation. However, the 2 cohorts differed, at baseline, with respect to several important ophthalmic characteristics such as mean visual acuity letter score, mean OCT-measured center point thickness, proportion of eyes with large cystoid spaces (>400 microns) at the center point as detected on OCT, mean area of retinal thickening as measured on color fundus photography and mean area of fluorescein leakage. All of these differences were in the direction of worse visual function and worse anatomy in CRVO participants compared with BRVO participants. Given the similar duration of macular edema in the two groups, these data suggest that CRVO is a disease that affects both anatomy and visual function more adversely than BRVO. One exception is the finding that the mean area of capillary non-perfusion measured greater among BRVO than CRVO participants (Table 4 [available at <http://aaojournal.org>]); this may be due to the larger mean area of retinal hemorrhage (which may obscure visualization of capillary nonperfusion) in CRVO participants compared with BRVO participants.

These differences between the two cohorts with respect to demographics and ophthalmic characteristics are consistent with what has been reported previously among patients with retinal vein occlusion. For example, in the Eye Disease Case-control Study (EDCCS) (CRVO, N=258; BRVO, N=270), diabetes mellitus was found to be a risk factor for CRVO, but not BRVO.^{22,23} The CVOS group M (eyes with CRVO and macular edema) included 155 eyes with a median baseline visual acuity of 20/160 in treated eyes and 20/125 in control eyes.⁵ In the BVOS (group III study – eyes with macular edema, N=139), 56 (79%) treated eyes and 54 (79%) control eyes had a baseline visual acuity between 20/40 and 20/100.¹ It is, therefore, not surprising that eyes in the CRVO trial had a lower mean baseline visual acuity letter score, a higher mean OCT-measured center point thickness, a larger mean area of retinal thickening measured on fundus photographs, and a larger mean area of fluorescein leakage compared with eyes in the BRVO trial. The difference in severity of disease between CRVO and BRVO supports the SCORE Study statistical plan to analyze the CRVO and BRVO cohorts as separate trials rather than combining them both into one cohort for analysis.

To examine the comparability of the SCORE Study results to those of prior clinical trials, we compared the baseline characteristics of the SCORE Study participants with baseline characteristics from other studies that have evaluated participants with retinal vein occlusion. The comparison below includes participants from the CVOS (group M study)⁵, BVOS (group III study)¹ and the Eye Disease Case-control Study.^{22,23}

With respect to race, 91% of participants in the SCORE CRVO trial and 88% of participants in the SCORE BRVO trial were white. In the EDCCS, 72% of participants with CRVO and 73% of participants with BRVO were white. The CVOS group M cohort was 94% white. Racial demographics were not reported for the BVOS group III cohort. The mean age of participants was 68 years in the SCORE CRVO trial and 67 years in the SCORE BRVO trial. Sixty percent of the CRVO cohort and 71% of the BRVO cohort in the EDCCS were between the ages of 55-74 (inclusive) at baseline. The mean age of participants in the CVOS group M cohort was 67 years. In the BVOS, 71% of participants were between the ages of 60-79 years (inclusive).

In the SCORE Study, 71% of CRVO participants and 70% of BRVO participants had a self-reported history of hypertension. In the EDCCS, 65% of participants with CRVO had a history of hypertension and 75% of participants with BRVO had a history of hypertension. In the CVOS, 57% of participants were reported to be taking medication for hypertension or had elevated blood pressure at baseline. In the BVOS, 44% of participants had a history of hypertension defined as taking medication for hypertension before study entry.

In the SCORE Study, 22% of CRVO participants and 14% of BRVO participants had a history of diabetes mellitus. In the EDCCS, 17% of participants with CRVO and 15% of participants with BRVO had a history of diabetes mellitus. In the CVOS, 7% of participants had a history of diabetes mellitus and in the BVOS, 4% of participants had a history of diabetes mellitus.

With regard to ophthalmic characteristics, a comparison of the SCORE CRVO cohort to the CVOS demonstrates that the SCORE CRVO cohort had a shorter mean disease duration and larger areas of retinal thickening on color fundus photography than the cohort in the CVOS, but the cohorts were generally similar. In the CVOS group M, 3% of eyes had <2 disc areas of macular edema, 36% of eyes had 2 to <5 disc areas of macular edema and 61% of eyes had 5 or more disc areas of macular edema. The SCORE CRVO participants had a mean area of retinal thickening of 12.3 disc areas in the grid on color fundus photography and the categorical breakdown for the SCORE CRVO trial shows larger areas of retinal thickening compared with the CVOS group M (data not shown). In terms of disease duration, 97% of CRVO participants in the SCORE Study had a duration of 12 months or less compared with 60% of CVOS group M participants with this duration of disease. The distribution of visual acuity at baseline

between the 2 studies was similar; 78% of participants in the SCORE CRVO trial and 82% of participants in the CVOS had a baseline visual acuity of between 20/50-20/200 (inclusive).

A comparison of the BRVO cohort in the SCORE Study to the BVOS also demonstrates a number of similarities between the cohorts with regard to ophthalmic characteristics. In the SCORE BRVO trial, 59% of participants had a disease duration of between 3 and 12 months (inclusive). Fifty-seven percent of participants in the BVOS had this disease duration. The distribution of visual acuity at baseline was similar for the SCORE BRVO cohort and the BVOS group III cohort: nearly half of the participants presented with a visual acuity between 20/40-20/50 and one-third of participants had a visual acuity between 20/70 and 20/100 in both cohorts.

Thus, the baseline demographic and ophthalmic characteristics of the SCORE Study participants are similar to those of participants in other clinical trials that have evaluated retinal vein occlusion. The CVOS and EDCCS were performed a decade ago and the BVOS was performed more than 2 decades ago. The similarities in baseline characteristics across all of these studies are remarkable given the improvement in diagnosis and management of systemic diseases, such as hypertension and diabetes mellitus, that have occurred in the years since the CVOS, BVOS and EDCCS were conducted.

The literature supports that the incidence and prevalence of diabetes mellitus^{31,32} and hypertension^{33,34} have increased in the last few decades in the United States. An increased prevalence of diabetes mellitus and hypertension in the general population should, all other things being equal, result in a higher prevalence of diabetes mellitus and hypertension in patients with CRVO and BRVO. We did not observe this phenomenon in the participant population in the SCORE Study, possibly implying that the risk of developing CRVO or BRVO secondary to diabetes mellitus and hypertension has declined. Two possible explanations for this declining risk are (1) improved medical management of diabetes mellitus and hypertension causes the risk to decline (2) more aggressive diagnosis of diabetes mellitus and hypertension means that healthier people are counted as having these diseases, but it is less likely that these healthier patients develop CRVO or BRVO.

The similarities between the different cohorts recruited over various geographic regions from a multitude of clinical sites, over different time periods and across different clinical trials (each with a different purpose and slightly different inclusion and exclusion criteria) suggest that the SCORE Study results, when available, will be applicable to a well characterized patient population with retinal vein occlusion. Additionally, differences, with respect to baseline ophthalmic characteristics, between cohorts with CRVO and BRVO in the CVOS, BVOS and the SCORE Study suggest that future clinical trials for retinal vein occlusion should continue to evaluate CRVO and BRVO as separate entities.

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TABLE 1
Study Eye Major Inclusion and Exclusion Criteria

<i>Inclusion criteria</i>	
•	Best corrected electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) visual acuity letter score of ≤ 73 (approximate Snellen equivalent of 20/40 or worse) and ≥ 19 (approximate Snellen equivalent of 20/400 or better). [<i>Note: the original lower limit of visual acuity was expanded from ≥ 34 letters to ≥ 24 letters 5 months after accrual began and then from ≥ 24 letters to ≥ 19 letters 12 months after accrual began</i>]
•	Center-involved macular edema due to central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) present on clinical examination
•	Mean central subfield retinal thickness (CST) of two optical coherence tomography (OCT) fast macular scans ≥ 250 microns
•	Media clarity, pupillary dilation, and subject cooperation sufficient for adequate fundus photographs
<i>Exclusion criteria</i>	
•	Presence of macular edema due to a cause other than CRVO or BRVO
•	Presence of an ocular condition such that visual acuity would not improve from resolution of the edema (e.g. foveal atrophy)
•	Substantial cataract estimated to have reduced visual acuity by 3 lines or more
•	Prior treatment with intravitreal corticosteroids at any time or peribulbar steroid injection within 6 months prior to randomization
•	History of focal/grid macular photocoagulation within 15 weeks (3.5 months) <i>or</i> panretinal photocoagulation within 4 months prior to randomization <i>or</i> anticipated need for PRP within the 4 months following randomization
•	Prior pars plana vitrectomy
•	Major ocular surgery (including cataract extraction) within prior 6 months or anticipated within the next 6 months following randomization
•	Yttrium Aluminum Garnet (YAG) capsulotomy performed within 2 months prior to randomization
•	Intraocular pressure (IOP) ≥ 25 mmHg, open-angle glaucoma (either primary open-angle glaucoma or other cause of open-angle glaucoma), steroid-induced IOP elevation that required IOP-lowering treatment or pseudoexfoliation
•	Aphakia

TABLE 2
Measurement and Examination Procedures for Scheduled Study Evaluations

Visit	E-ETDRS						Fundus photos**	FA	Injection/Laser [#]
	Medical history	Refraction	Visual acuity	OCT	IOP	Dilated fundus	Slit-lamp	Lens	
Baseline/randomization	X	X	X	X	X	X	X	X	X*
Safety: Day 4 and Month 1 after each injection			X*		X*	X*	X*		
Follow-up: At 4 months	X	X	X	X	X	X	X	X	X*
At 12 and 24 months	X	X	X	X	X	X	X	X	X*
At 8, 16, 20, 28 and 32 months		X	X	X*	X	X	X	X	X*
At 36 months	X	X	X	X	X	X	X	X	X*

E-ETDRS = electronic Early Treatment Diabetic Retinopathy Study. OCT = optical coherence tomography. IOP = intraocular pressure. FA = Fluorescein angiogram

[#] injection or laser given for applicable patients at baseline. At 4-month intervals, protocol-defined retreatment criteria dictated whether or not additional treatment was provided.

* refers to study eye only.

** For fundus photos, non-study eye had 3-field photos at baseline and at annual visits.

TABLE 3

Baseline Characteristics of SCORE Study Participants

Characteristic ¹	CRVO				BRVO			
	1 mg IVTA	4 mg IVTA	Std Care	Total	1 mg IVTA	4 mg IVTA	Std Care	Total
Number of participants	92	91	88	271	136	138	137	411
Demographic Characteristics								
Age (years)	67.4 (12.4)	67.5 (12.0)	68.0 (12.4)	67.2 (11.5)	68.1 (10.6)	66.9 (11.5)	67.4 (11.2)	
< 50 (%)	8 (9)	7 (8)	10 (11)	25 (9)	5 (4)	6 (4)	21 (5)	
50-60 (%)	17 (18)	17 (19)	9 (10)	43 (16)	23 (17)	32 (23)	36 (26)	91 (22)
60-70 (%)	24 (26)	25 (27)	20 (23)	69 (25)	45 (33)	37 (27)	35 (26)	117 (28)
70-80 (%)	26 (28)	30 (33)	29 (33)	85 (31)	42 (31)	49 (36)	44 (32)	135 (33)
>80 (%)	17 (18)	12 (13)	20 (23)	49 (18)	16 (12)	15 (11)	16 (12)	47 (11)
Women (%)	43 (47)	40 (44)	40 (45)	123 (45)	68 (50)	63 (46)	71 (52)	202 (49)
White ² (%)	84 (91)	82 (90)	81 (92)	247 (91)	115 (85)	123 (89)	124 (91)	362 (88)
Not Hispanic or Latino ³ (%)	87 (95)	82 (90)	77 (88)	246 (91)	120 (88)	131 (95)	121 (88)	372 (91)
Study Eye Characteristics⁴								
E-ETDRS visual acuity letter score (letters)	51.2 (14.5)	50.8 (14.5)	52.2 (13.1)	51.4 (14.0)	57.9 (11.9)	56.2 (13.4)	56.8 (13.0)	56.9 (12.7)
59-73 (20/40 to 20/63) (%)	34 (37)	34 (37)	34 (39)	102 (38)	74 (54)	71 (51)	70 (51)	215 (52)
49-58 (20/80 to 20/100) (%)	19 (21)	19 (21)	19 (22)	57 (21)	33 (24)	34 (25)	34 (25)	100 (24)
19-48 (20/125 to 20/400) (%)	39 (42)	38 (42)	35 (40)	112 (41)	29 (21)	34 (25)	33 (24)	96 (23)
Duration of macular edema (months)	4.5 (4.2)	4.2 (3.6)	4.2 (3.1)	4.3 (3.7)	4.1 (3.4)	4.6 (3.9)	4.5 (4.2)	4.4 (3.8)
<3 (%)	36 (39)	40 (44)	29 (33)	105 (39)	52 (38)	51 (37)	49 (36)	152 (37)
3-6 (%)	38 (41)	34 (37)	43 (49)	115 (42)	63 (46)	60 (43)	62 (45)	185 (45)
7-12 (%)	14 (15)	15 (16)	14 (16)	43 (16)	18 (13)	22 (16)	17 (12)	57 (14)
>12 (%)	4 (4)	2 (2)	2 (2)	8 (3)	3 (2)	5 (4)	9 (7)	17 (4)
Dense macular hemorrhage (%)	NA	NA	NA	NA	38 (28)	43 (31)	40 (29)	121 (29)
OCT central subfield ⁵ (microns)	598 (179)	580 (200)	609 (144)	595 (176)	495 (154)	483 (121)	497 (155)	491 (144)
Prior grid photocoagulation (%)	0 (0)	1 (1)	0 (0)	1 (0)	8 (6)	9 (7)	13 (9)	30 (7)
Prior sector/panretinal photocoagulation (%)	0 (0)	0 (0)	2 (2)	2 (1)	1 (1)	1 (1)	3 (1)	3 (1)
Intraocular pressure (mmHg)	15.2 (3.2)	15.8 (3.2)	15.4 (3.3)	15.5 (3.2)	15.0 (2.8)	15.1 (3.1)	15.2 (3.1)	15.1 (3.0)
Phakic (%)	77 (84)	76 (84)	66 (75)	219 (81)	109 (80)	110 (80)	115 (84)	334 (81)
Nuclear opacity present (% of phakic eyes)	68 (88)	68 (89)	50 (76)	186 (85)	87 (80)	95 (86)	87 (76)	269 (81)
Cortical opacity present (% of phakic eyes) ⁶	24 (31)	25 (33)	22 (33)	71 (32)	30 (28)	35 (32)	15 (13)	80 (24)
Posterior subcapsular opacity present (% of phakic eyes)	8 (10)	8 (11)	3 (5)	19 (9)	14 (13)	11 (10)	11 (10)	36 (11)
Other Clinical Characteristics								
Diabetes mellitus (%)	16 (18)	22 (24)	22 (25)	60 (22)	17 (13)	24 (17)	16 (12)	57 (14)
Hypertensive (%)	62 (67)	61 (67)	69 (78)	192 (71)	94 (69)	95 (69)	97 (71)	286 (70)
Coronary artery disease (%)	16 (17)	19 (21)	19 (22)	54 (20)	26 (19)	27 (20)	19 (14)	72 (18)
History of cancer (%)	18 (20)	24 (26)	14 (16)	56 (21)	21 (15)	27 (20)	23 (17)	71 (17)

CRVO = central retinal vein occlusion. BRVO = branch retinal vein occlusion. IVTA = intravitreal triamcinolone acetate. E-ETDRS = electronic Early Treatment Diabetic Retinopathy Study. OCT = optical coherence tomography.

¹ Mean (Std Dev) unless otherwise noted

² In the same column order as given for White, the numbers are Asian: 1, 2, 0, 3, 3, 3, 2, 8; Black: 5, 3, 3, 11, 13, 9, 6, 28; Native Hawaiian or other Pacific Islanders: 0, 2, 0, 2, 0, 0, 0; unable to specify: 0, 2, 4, 6, 4, 0, 2, 6; and more than one race: 2, 0, 0, 2, 1, 3, 7.

³ In the same column order as given for Not Hispanic or Latino, the numbers are Hispanic or Latino: 4, 4, 10, 18, 14, 2, 10, 26 and unknown: 1, 5, 1, 7, 2, 5, 6, 13.

⁴ Emboldened entries indicate across-disease comparisons significant at $p \leq 0.05$ after Hochberg correction for multiple testing.

⁵Two OCT images were obtained at screening from each eye and the mean of two central subfield measurements used for eligibility.

⁶Standard care group with fewer cortical opacities than triamcinolone groups in BRVO trial ($p=.0025$, $p^*=0.22$)

Baseline Image Characteristics of the Study Eye of Score Study Participants: Reading Center Assessment

TABLE 4

Characteristic ¹	CRVO				BRVO			
	1 mg IVTA ⁴	4 mg IVTA ⁴	Std Care	Total	1 mg IVTA ⁴	4 mg IVTA ⁴	Std Care	Total
<i>Color Photographs³</i>								
Number of images evaluated	91	90	85	266	133	132	133	398
Area of retinal thickening (DA ²)								
inner zone	3.7 (0.8)	3.6 (0.7)	3.7 (0.9)	3.7 (0.8)	2.7 (0.9)	2.6 (0.8)	2.6 (0.8)	2.6 (0.8)
grid	12.1 (4.8)	11.9 (5.0)	12.9 (4.6)	12.3 (4.8)	7.8 (3.0)	7.4 (2.8)	7.4 (2.7)	7.5 (2.8)
Missing	3	5	2	10	1	1	2	4
Area of retinal hemorrhage (DA)								
inner zone	0.7 (0.8)	0.8 (0.9)	0.8 (0.8)	0.7 (0.8)	0.7 (0.7)	0.8 (0.7)	0.8 (0.7)	0.8 (0.7)
grid	3.1 (3.2)	3.4 (3.5)	3.6 (3.1)	3.4 (3.3)	2.8 (2.4)	2.9 (2.4)	3.2 (2.5)	2.9 (2.4)
Missing	2	0	2	4	1	0	1	2
<i>OCT³</i>								
Number of images evaluated	90	89	86	265	131	135	136	402
Center Point ⁴ (microns)	636(217)	641(248)	693(209)	656(226)	526(197)	514(160)	535(200)	525(186)
<326 (%)	10(11)	7(8)	4(5)	21(8)	17(13)	13(10)	16(12)	46(11)
326-425 (%)	6(7)	9(10)	1(1)	16(6)	24(18)	27(20)	28(20)	79(20)
426-525 (%)	11(12)	13(14)	7(8)	31(12)	32(24)	37(27)	32(23)	101(25)
526-625 (%)	14(16)	19(21)	20(23)	53(20)	22(17)	27(20)	25(18)	74(18)
626-725 (%)	14(16)	12(13)	23(27)	49(18)	20(15)	20(15)	12(9)	52(13)
726-825 (%)	22(24)	9(10)	12(14)	43(16)	9(7)	10(7)	28(7)	47(12)
>825	13(14)	20(22)	18(21)	51(19)	8(6)	3(2)	14(10)	25(6)
Missing/cannot grade (%)	0(0)	1(1)	1(1)	2(1)	0(0)	0(0)	0(0)	0(0)
<i>Size of cystoid spaces at center point (microns)</i>								
Absent	13(14)	12(13)	7(8)	32(12)	18(14)	22(16)	32(23)	72(18)
<= 200	10(11)	13(14)	10(12)	33(12)	34(26)	29(21)	27(20)	90(22)
<= 400	36(40)	38(42)	34(40)	108(41)	53(41)	61(45)	58(42)	173(43)
> 400	31(34)	26(29)	35(41)	92(35)	25(19)	23(17)	19(14)	67(17)
Missing	0	1(1)	0	1(0)	1(1)	1(1)	1(1)	3(1)
<i>Cystoid abnormalities</i>								
None (%)	3(3)	2(2)	1(1)	6(2)	0(0)	1(1)	1(1)	2(0)
Mild (%)	9(10)	8(9)	3(3)	20(8)	16(12)	18(13)	29(21)	63(16)
Moderate (%)	9(10)	11(12)	10(12)	30(11)	11(8)	15(11)	10(7)	36(9)
Severe (%)	68(76)	66(73)	69(80)	203(76)	102(77)	98(72)	94(69)	294(73)
Questionable/Cannot grade (%)	1(1)	3(3)	3(3)	7(3)	3(2)	4(3)	3(2)	10(2)
<i>Subretinal fluid</i>								
None (%)	40(44)	44(49)	30(35)	114(43)	73(55)	82(60)	81(59)	236(58)
Questionable/definite, spares center (%)	15(17)	6(7)	18(21)	39(15)	17(13)	17(13)	14(10)	48(12)
Definite, center involved (%)	32(36)	37(41)	36(42)	105(39)	38(29)	36(26)	39(28)	113(28)
Missing/cannot grade (%)	3(3)	3(3)	2(2)	8(3)	4(3)	1(1)	3(2)	8(2)
<i>Vitreoretinal interface abnormalities</i>								
None (%)	62(69)	57(63)	61(71)	180(68)	102(77)	93(68)	97(71)	292(72)
Questionable (%)	13(14)	15(17)	14(16)	42(16)	13(10)	19(14)	25(18)	57(14)
Definite (%)	13(14)	16(18)	11(13)	40(15)	14(11)	21(15)	13(9)	48(12)
Missing/cannot grade (%)	2(2)	2(2)	0(0)	4(2)	3(2)	3(2)	2(1)	8(2)
Total macular volume (mm ³)	10.6 (2.0)	10.0 (2.1)	10.5 (1.7)	10.4 (2.0)	10.0 (2.1)	9.5 (1.6)	9.6 (1.8)	9.7 (1.8)
Missing	28	42	38	109	62	58	65	185
<i>Fluorescein Angiogram³</i>								
Number of images evaluated	91	89	86	266	133	136	137	406
Area of fluorescein leakage (DA)								

Characteristic ¹	CRVO				BRVO			
	1 mg IVTA	4 mg IVTA	Std Care	Total	1 mg IVTA	4 mg IVTA	Std Care	Total
inner zone	3.5 (0.8)	3.5 (0.8)	3.7 (0.7)	3.6 (0.8)	2.0 (0.7)	2.0 (0.8)	2.0 (0.7)	2.0 (0.7)
Grid	10.9 (5.0)	10.5 (5.0)	11.6 (4.8)	11.0 (4.9)	6.2 (2.3)	6.0 (2.5)	6.2 (2.4)	6.1 (2.4)
Missing	3	5	3	11	2	3	2	7
Area of capillary loss (DA)								
inner zone	0.1 (0.3)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.2 (0.4)	0.1 (0.4)	0.1 (0.3)	0.2 (0.4)
Missing	20	24	25	69	31	28	33	92
Grid	0.2 (0.9)	0.2 (0.8)	0.1 (0.3)	0.2 (0.7)	0.8 (1.6)	0.6 (1.3)	0.5 (1.3)	0.6 (1.4)
Missing	20	24	25	69	30	28	32	90
> 5 DA of capillary loss in the eye (%)	2(2)	2(2)	0(0)	4(2)	17(13)	12(9)	12(9)	41(10)
> 10 DA of capillary loss in the eye (%)	2(2)	1(1)	0(0)	3(1)	13(10)	7(5)	6(4)	26(6)
Not done	19(21)	24(27)	28(33)	71(27)	38(29)	35(26)	41(30)	114(28)

CRVO = central retinal vein occlusion. BRVO = branch retinal vein occlusion. IVTA = intravitreal triamcinolone acetate. DA=disc areas. OCT = optical coherence tomography.

¹ Mean (Std Dev) unless otherwise noted.

² Disc areas.

³ Emboldened entries indicate across-disease comparisons significant at $p^* \leq 0.05$ after Hochberg correction for multiple testing.

⁴ 29% of OCT images were manually measured for center point thickness. The percentage did not differ significantly within each trial or between trials.