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SCORE2 Report 2

Study Design and Baseline Characteristics

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Purpose: 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 noninferior to intravitreal aflibercept for treatment of decreased vision attributable to macular edema associated with central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO).

Participants: Total of 362 participants: 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 with 11% of CRVO patients (*P* value adjusted for multiple testing = 0.0001). This is similar to findings from the previous SCORE Study. Comorbidities included hypertension (77%), diabetes mellitus (31%), and coronary artery disease (15%). At baseline, mean visual acuity letter score was 50 (20/100) (range, 19−73 [20/400 to 20/40]), mean optical coherence tomography (OCT)−measured central subfield thickness was 678 μm (range, 300−1203 μm), and mean number of months from diagnosis of macular edema to randomization was 6 (range, 0−104 months). One hundred twenty (33%) SCORE2 participants had been treated previously with anti−vascular endothelial growth factor (anti-VEGF) therapy, with these participants having baseline visual acuity letter score and OCT-measured central subfield thickness similar to those without prior anti-VEGF treatment, but longer mean duration of macular edema before randomization (18 months vs. 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-naïve 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. *Ophthalmology 2016;■:1−12 © 2016 by the American Academy of Ophthalmology*

Retinal vein occlusion (RVO) is the most common retinal vascular disorder after diabetic retinopathy, affecting 1% to 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 RVO.[4−6] Although many treatment options have been investigated for decreased vision attributable to macular edema associated with central RVO (CRVO),[7−16] the ***S***tandard Care versus ***CO***rticosteroid for ***RE***tinal Vein Occlusion (SCORE) Study, sponsored by the National Eye Institute, 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 (VEGF) therapy for the treatment of decreased vision due to CRVO-associated macular edema; the Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety (CRUISE) trial[18] Study demonstrated favorable visual outcomes associated with the use of intravitreal ranibizumab, and the VEGF Trap-Eye for macular edema secondary to CRVO (COPERNICUS)[19] and VEGF Trap-Eye: Investigation of Efficacy and Safety in CRVO (GALILEO) [20] studies demonstrated favorable visual outcomes associated with the use of intravitreal aflibercept. In addition, numerous case reports and small randomized clinical trials demonstrating favorable visual

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acuity outcomes following intravitreal bevacizumab in patients with decreased vision attributable to macular edema secondary to CRVO were published.[15,21–30]

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

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[32] and diabetic macular edema.[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 placenta-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] The ***S***tudy of ***CO***mparative Treatments for ***RE***tinal Vein Occlusion 2 (SCORE2) study is designed to determine whether bevacizumab is noninferior 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 to explore 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.

Methods

Study Synopsis

SCORE2 is a multicenter, prospective, randomized, phase III clinical trial designed to determine whether bevacizumab is noninferior 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 noninferiority margin is set at an ETDRS visual acuity letter score of 5, as measured by the electronic ETDRS (E-ETDRS) visual acuity test. Secondary efficacy outcomes are based on visual acuity testing, spectral-domain (SD) optical coherence tomography (OCT), fundus photography, ultrawide-field fluorescein angiography (FA), 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 noninferiority comparison between the 2 groups was 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 or changing to a treat-and-extend (TAE) regimen. 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 or 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 because it was deemed more likely that participants who fail to respond 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 (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 had received Ophthalmic Clinical Trial Training and Certification (The Emmes Corporation, Rockville, MD). Photographers performing FA were trained and certified by Optos (Dunfermline, 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 1 eye to the study. Table 2 summarizes the major ocular inclusion and exclusion criteria.

Screening and Primary Randomization

Prospective participants first consented to screening and then were 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 grading was used); (3) ultra-widefield 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 E-ETDRS visual acuity at 3 meters by a