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Baseline Characteristics and Response to Treatment of Participants with HRVO Compared to Participants with BRVO and Participants with CRVO in the SCORE Study:

SCORE Study Report 14

Ingrid U. Scott, MD, MPH¹, Paul C. VanVeldhuisen, PhD², Neal L. Oden, PhD², Michael S. Ip, MD³, Amitha Domalpally, MD³, Bernard H. Doft, MD⁴, Michael J. Elman, MD⁵, Barbara A. Blodi, MD³, and SCORE Study Investigator Group

¹Departments of Ophthalmology and Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania; ²The EMMES Corporation, Rockville, Maryland; ³University of Wisconsin, Madison, Wisconsin; ⁴Retina Vitreous Consultants, Pittsburgh, Pennsylvania; ⁵Elman Retina Group, Baltimore, Maryland.

Abstract

Objective: To compare baseline characteristics and treatment response of participants with hemiretinal vein occlusion (HRVO) with those of participants with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) in the SCORE Study.

Methods: Eyes were randomized to standard care (SC), 1mg intravitreal triamcinolone, or 4mg intravitreal triamcinolone. SC was observation in the SCORE-CRVO trial and grid photocoagulation in the SCORE-BRVO trial. HRVO eyes were enrolled into the SCORE-BRVO trial. Baseline characteristics, changes in visual acuity (VA) and center point thickness (CPT), safety outcomes, and number of treatments were compared among HRVO, BRVO, and CRVO participants.

Results: At baseline, HRVO eyes were intermediate between BRVO and CRVO eyes in area of retinal thickening, fluorescein leakage area, VA, and CPT. No differences in VA change from baseline to 1 year were noted between SC groups for HRVO and BRVO. Within triamcinolone-treated eyes, HRVO eyes did not differ from BRVO eyes in VA change, but HRVO eyes fared better than CRVO eyes. There were no differences in CPT change between SC groups for HRVO and BRVO, nor were there differences across the three disease entities for triamcinolone-treated eyes. There were no differences in frequency of protocol treatments and adverse events.

Conclusions: HRVO participants were similar to BRVO and CRVO participants regarding most demographic characteristics, with fundus findings intermediate between BRVO and CRVO. HRVO eyes responded to treatment similarly to BRVO eyes, and there was no difference among the three disease entities in frequency of protocol treatments and adverse events.

Correspondence and request for reprints to: Paul C. VanVeldhuisen, PhD, The EMMES Corporation, 401 N. Washington St. Suite 700, Rockville, MD 20850, Telephone: 301-251-1161; Fax: 301-251-1355; score@emmes.com.

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INTRODUCTION

Retinal venous occlusive disease is estimated to be the second most common cause of retinal vascular disease in the United States.¹ Retinal vein occlusions may be classified according to the site of occlusion as branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), or hemiretinal vein occlusion (HRVO). Some researchers have subclassified HRVO into hemicentral retinal vein occlusion (HCRVO), in which a dual-trunked central retinal vein persists in the anterior part of the optic nerve as a congenital variant and one of the trunks is occluded, and hemispheric retinal vein occlusion (HSRVO), in which a major branch of the central retinal vein is occluded at or near the optic disc.^{2–6} Some of these authors have concluded that most HRVO are of the hemicentral retinal vein occlusion subtype and, thus, closely related to CRVO and unrelated to BRVO.⁴ Others have argued that most HRVO are of the hemispheric retinal vein occlusion variety and are, thus, much more related to BRVO.⁷ However, use of this subclassification of HRVO has been limited because of controversy about the importance of such subgrouping and difficulties in identifying the site of occlusion in many eyes with HRVO.^{7,8} Risk factors, clinical features, and systemic associations have been reported to differ among patients with BRVO, CRVO, and HRVO.^{2,9} Moreover, phase III randomized controlled clinical trials have demonstrated that the response to laser treatment and the response to intravitreal triamcinolone differ between eyes with macular edema associated with CRVO compared to eyes with macular edema associated with BRVO.^{1,10–12} The purpose of the current study is to compare the baseline characteristics and treatment response of participants with HRVO with those of participants with BRVO and participants with CRVO in the Standard Care versus COrticosteroid for REtinal Vein Occlusion (SCORE) Study.

METHODS

The SCORE Study design and methods are described in detail elsewhere¹³ and summarized here. The study adhered to the tenets of the Declaration of Helsinki. Institutional Review Board (IRB) approval for the protocol was obtained from either a central IRB (Jaeb Center for Health Research) or from institutional IRBs, and informed consent was obtained from all participants prior to eligibility screening and again prior to randomization into the study. Definitions of BRVO, CRVO, and HRVO based on clinical examination findings were specified in the SCORE Study protocol (Table 1). The eligible eye of each participant was randomized to one of three equally-sized parallel arms in either the BRVO trial or the CRVO trial; standard care (SC), 1 mg intravitreal triamcinolone, and 4 mg intravitreal triamcinolone. Study drug was manufactured as a sterile, preservative-free, single-use, intravitreal injectable (Allergan Inc, Irvine, California; 4-mg brand name, Trivaris). Participants in the CRVO trial assigned to SC were observed. Participants in the BRVO trial assigned to SC were treated with grid photocoagulation if a dense macular hemorrhage did not preclude treatment. If a dense hemorrhage was present, grid photocoagulation was postponed until clearing of the hemorrhage permitted grid photocoagulation treatment. Participants presenting with HRVO were enrolled into the BRVO trial. Participants were treated with the randomly assigned treatment at baseline and at 4-month intervals except when study-defined criteria to defer additional treatment or to employ the alternate treatment regimen were satisfied. 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 closeout date of February 28, 2009.

Study visits were scheduled every 4 months following randomization. At all 4-month study visits, participants had visual acuity testing at 3 meters (including manifest refraction using the electronic Early Treatment of Diabetic Retinopathy Study [E-ETDRS] visual acuity testing method¹⁴), intraocular pressure (IOP) measurement, an eye examination and an optical coherence tomography (OCT) scan. 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. Fluorescein angiography (FA) was performed at baseline, 4 months, 12 months and 24 months. All imaging tests (color fundus photographs, FA and OCT) were sent to the University of Wisconsin Fundus Photograph Reading Center (Reading Center). Classification of retinal vein occlusion for the purposes of the analyses in this paper was based on assessments by clinical site SCORE Study investigators prior to randomization. Of note, investigator and Reading Center agreement in classifying disease status was excellent in the SCORE Study.¹⁵ The SCORE Study has been registered with clinicaltrials.gov (Identifier: NCT00105027).

Statistical Methods

Both discrete and continuous variables were examined to assess whether baseline characteristics of HRVO participants match more closely with characteristics of BRVO or CRVO participants, or whether characteristics of HRVO participants are more intermediate between the other two disease entities. For discrete baseline variables (e.g., gender), two-way contingency tables were constructed cross-classifying disease status (i.e., HRVO versus BRVO and HRVO versus CRVO) with discrete baseline characteristics. Chi-square statistics were divided by the sample size to allow meaningful HRVO/BRVO and HRVO/CRVO comparisons, with a Chi-square test statistic close to zero indicating that the distributions being studied are similar (Table 2). For continuous baseline variables (e.g., age), the empirical distribution function (EDF) was examined (EDF is a function that displays the cumulative distribution of the variable that increases by $1/n$ at the n^{th} data point). The Kolmogorov-Smirnov statistic, which measures the maximum deviation of the EDF within the disease classification from the pooled EDF, was used to compare HRVO versus BRVO and HRVO versus CRVO (Table 3). A Kolmogorov-Smirnov test statistic close to zero indicates that the distributions being studied are similar. To control type 1 error, results were deemed statistically significant at $p < 0.05$ after a Hochberg adjustment.

To assess whether the response to treatment of HRVO participants match more closely with BRVO or CRVO participants, generalized estimating equations (GEE) were fit for the dependent variables of change from baseline in visual acuity letter score and center point thickness (CPT) based on OCT at the 4-, 8-, and 12-month visits. In these models, an autoregressive correlations structure was assumed, and the baseline measure (e.g., screening visual acuity letter score or baseline center point thickness, depending on the dependent variable in the model) and visit were adjusted for the model.

RESULTS

The SCORE Study included 59 HRVO participants, 352 BRVO participants, and 271 CRVO participants. Tables 1 and 2 present data on whether baseline characteristics of HRVO participants match more closely with characteristics of BRVO or CRVO participants, or whether the baseline characteristics of HRVO participants are more intermediate between the other two disease entities. With respect to discrete baseline variables (Table 2), no comparisons for BRVO versus HRVO participants were significant after Hochberg adjustment, indicating similarities among these characteristics. Comparing CRVO versus HRVO participants, after adjustment, two comparisons were statistically significant: race ($p_{\text{unadjusted}}=0.001$; $p_{\text{hochberg}}=0.004$) and prior grid laser photocoagulation ($p_{\text{unadjusted}}=0.0003$; $p_{\text{hochberg}}=0.01$). For race, HRVO had a higher prevalence of black participants (16.9%) than CRVO (4.1%). The prevalence of blacks was also lower for BRVO participants (5.1%) compared to HRVO participants, but not significantly ($p_{\text{hochberg}}=0.12$). Further, HRVO participants were more likely to have had prior grid laser photocoagulation (6.8%) compared with CRVO participants (0.4%).

For continuous baseline variables (Table 3), the HRVO distribution for two variables differed statistically from both CRVO and BRVO: disc areas of retinal thickening on fundus photography ($p_{\text{unadjusted}}<0.0001$; $p_{\text{hochberg}}=0.01$) and leakage in the grid based on fluorescein angiography ($p_{\text{unadjusted}}<0.0001$; $p_{\text{hochberg}}=0.01$). For both these variables, HRVO eyes were intermediate between BRVO and CRVO eyes, with BRVO eyes having the least amount of disc areas of retinal thickening (7.2 versus 9.5 for HRVO and 12.3 for CRVO) and disc areas of leakage in the grid (5.8 versus 8.2 for HRVO and 10.9 for CRVO).

Response to treatment of HRVO participants was examined based on change from baseline in visual acuity letter score and center point thickness based on OCT at the 4-, 8-, and 12-month visits. For the standard care (SC) assignment groups, HRVO eyes were compared only to BRVO eyes, since the treatment regimen for these eyes were the same, with grid photocoagulation postponed, if necessary, until clearing of hemorrhage permitted grid photocoagulation treatment. Both SC groups showed improvements in visual acuity letter score over time, with a mean improvement of 6.3 in visual acuity letter score for HRVO eyes and 3.8 in visual acuity letter score for BRVO eyes at month 12 (Table 4). Based on GEE regression models, no differences in mean change in visual acuity letter score were noted over 12 months between the SC groups for these two disease entities ($p=0.96$; Table 4).

Within those eyes randomized to receive steroid injections, all 3 disease entities were compared, as the treatment regimen for participants randomized to intravitreal steroid injections was the same. Due to the similarities in the visual acuity and OCT outcomes between participants randomized to 1 mg and 4 mg reported previously,^{11,12} this analysis combined eyes assigned to 1 mg and 4 mg. Both HRVO and BRVO eyes that received intravitreal steroid injections showed improvements in mean visual acuity letter score through month 12, with a mean improvement of 8.8 in visual acuity letter score for HRVO eyes and 4.5 in visual acuity letter score for BRVO eyes at month 12 (Table 5). However, CRVO eyes on average lost visual acuity over time, with a mean decrease of 1.4 letters at month 12. When comparing outcomes for the intravitreal steroid groups across the 3 disease

areas over 12 months, there was an overall difference for change from baseline in visual acuity letter score ($p<0.0001$). Considering pairwise tests, BRVO eyes did not differ from HRVO eyes in change from baseline in visual acuity letter score over 12 months ($p=0.09$), but CRVO eyes fared significantly worse than HRVO eyes ($p<0.0001$).

Tables 6 and 7 present the mean change from baseline in center point thickness based on OCT for the HRVO and BRVO SC groups (Table 6) and the intravitreal steroid injections groups for all 3 disease entities (Table 7). All show marked mean decreases from baseline in center point thickness, with the reduction increasing with time. However, there were no statistically significant differences in mean change from baseline in center point thickness between the SC groups ($p=0.60$) for HRVO and BRVO, nor were there differences for those eyes randomized to receive intravitreal steroids across the 3 disease entities ($p=0.20$).

The safety profile related to cataract and IOP through month 12 was compared across the 3 disease groups in Table 8. As reported previously,^{11,12} differences in these two safety outcomes differed between the 1 mg and 4 mg intravitreal injection groups, and so outcomes were examined within the 2 different doses. Cataract progression and cataract surgery did not differ among the 3 groups in the 1 mg and 4 mg groups. Furthermore, the proportion of eyes with an IOP increase ≥ 10 mm Hg over baseline was similar across the disease groups in the 1 mg compared with the 4 mg group, although there was an overall difference in the proportion initiating IOP-lowering medication in the 1 mg group ($p=0.01$ based on an overall chi-square test). The difference was not significant ($p=0.10$) when limiting the comparison of HRVO eyes (19%) to BRVO eyes (7%).

The data were examined to determine whether HRVO study eyes received a similar frequency of protocol treatments prior to 12 months compared with CRVO and BRVO study eyes. The mean number of grid laser photocoagulation treatments was approximately 1.5 in both the HRVO and BRVO groups (Table 9). For intravitreal injections, on average approximately 2 injections were given prior to 12 months in the HRVO study eyes for both the 1 mg and 4 mg arms, similar to that in CRVO and BRVO study eyes (Table 10).

COMMENT

In the SCORE Study, HRVO participants were similar to BRVO and CRVO participants in terms of age, gender, disease duration, visual acuity, and all comorbid conditions investigated. It is unclear why the prevalence of blacks was significantly higher among HRVO than CRVO participants. The higher likelihood of HRVO participants to have had prior grid laser compared to CRVO participants is likely due to treating ophthalmologists applying the results of the Branch Vein Occlusion Study (BVOS)¹ to patients with HRVO. While the BVOS demonstrated a visual acuity benefit of grid laser treatment in eyes with macular edema associated with BRVO,¹ the Central Vein Occlusion Study¹⁰ found no visual acuity benefit of grid laser treatment in eyes with macular edema associated with CRVO and, thus, eyes with CRVO were unlikely to have been treated previously with grid laser.

At baseline, HRVO eyes in the SCORE Study were intermediate between BRVO and CRVO eyes with respect to disc areas of retinal thickening and disc areas of fluorescein leakage.

The definitions of HRVO, BRVO and CRVO used by the clinical investigators in the SCORE Study protocol are listed in Table 1.¹³ The protocol definitions place HRVO as roughly intermediate between BRVO and CRVO with respect to the area of fundus involved. The results of the current study suggest that the clinical investigators adhered closely to the protocol definitions when assigning the type of vein occlusion to study eyes.

With regard to response to treatment, both HRVO and BRVO eyes in the SC and intravitreal triamcinolone groups showed improvement in mean visual acuity through month 12, with no significant difference between HRVO and BRVO eyes. In contrast, CRVO eyes treated with intravitreal triamcinolone, on average, lost visual acuity over time. This may be due to the poorer visual prognosis associated with CRVO compared to BRVO, likely due to a larger injured area of retina in CRVO compared to BRVO (e.g. involvement of the whole macula rather than just part of the macula).^{1,10} Despite the fact that CRVO eyes fared worse in terms of visual acuity outcome compared to HRVO and BRVO eyes, there was no statistically significant difference among the three disease entities with respect to change in OCT-measured center point thickness over 12 months. This finding is consistent with a previous SCORE Study publication, which reported that there is only a moderate correlation between OCT-measured thickness and visual acuity in patients with retinal vein occlusion,¹⁶ and points out that macular edema is only one mechanism of visual acuity loss in patients with RVO.

As discussed above, there is controversy with respect to whether HRVO is more commonly a hemicentral retinal vein occlusion (where HRVO would be more related to CRVO) or a hemispheric retinal vein occlusion (where HRVO would be more related to BRVO). The similarity of HRVO and BRVO when managed with either SC or intravitreal triamcinolone, and the differences between HRVO and CRVO when managed with intravitreal triamcinolone, suggest that HRVO may be more similar to BRVO than CRVO with respect to clinical characteristics. Conclusions regarding the pathophysiology of each entity cannot be made based on SCORE Study data since the Reading Center was unable to consistently identify the site of occlusion as being pre or post laminar.

A limitation of the current study is that it includes only 59 HRVO study participants, thereby impacting our ability to detect statistically significant differences when comparing characteristics of HRVO participants with those of BRVO and CRVO participants. For example, for baseline center point thickness (CPT) based on OCT, HRVO eyes had a mean thickness of 560 μm , a value in between the mean center point thickness of 520 μm for BRVO eyes and 659 μm for CRVO eyes. However, after adjustment for multiple comparisons, these pairwise differences comparing HRVO eyes with both BRVO and with CRVO eyes were not significant. In addition, at baseline, HRVO eyes had a mean visual acuity letter score that was intermediate between BRVO and CRVO eyes, but again, not statistically significantly different from the two other disease entities.

It should also be noted that, in the SCORE Study, attempts were made to include only perfused retinal vein occlusions, which limits the generalizability of SCORE Study results. For example, investigators were instructed to enroll only patients who the investigators believed had perfused retinal vein occlusions, patients needed to have a baseline best-

corrected ETDRS visual acuity of 73 (approximate Snellen equivalent, 20/40 or worse) and 19 (approximate Snellen equivalent, 20/400 or better), and eyes that, in the investigator's opinion, would not benefit from resolution of macular edema (such as eyes with macular ischemia) were not eligible for the SCORE Study. Visual outcomes of nonperfused retinal vein occlusions have been reported to be worse than those of perfused retinal vein occlusions.^{17,18}

In summary, in the SCORE Study, participants with HRVO were similar to BRVO and CRVO participants with respect to most demographic characteristics, with fundus findings intermediate between those of BRVO and CRVO. In the SCORE Study, HRVO was treated as BRVO; HRVO eyes responded to treatment similarly to BRVO eyes and there was no difference among the three disease entities with respect to frequency of protocol treatments and adverse events.

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As the Principal Investigator for the Data Coordinating Center I, Paul C. VanVeldhuisen, Ph.D., have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1:

Definitions of Retinal Vein Occlusion Type Provided to Clinicians in the Standard Care versus *C*orticosteroid for *R*etinal Vein Occlusion (SCORE) Study Protocol

Retinal Vein Occlusion Type	Definition in the SCORE Study Protocol
Branch	An eye that has retinal hemorrhage or other biomicroscopic evidence of retinal vein occlusion (e.g., telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in 1 quadrant of retina drained by the affected vein.
Hemiretinal	An eye that has retinal hemorrhage or other biomicroscopic evidence of retinal vein occlusion (e.g., telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in >1 quadrant but < all 4 quadrants. Typically, an HRVO is a retinal vein occlusion that involves 2 altitudinal quadrants.
Central	An eye that has retinal hemorrhage or other biomicroscopic evidence of retinal vein occlusion (e.g., telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in all 4 quadrants.

Table 2: HRVO Study Eyes Compared with BRVO and CRVO Study Eyes: Baseline Demographics for Discrete Variables

Total		BRVO		HRVO		CRVO		BRVO versus HRVO		CRVO versus HRVO	
		N	%	N	%	N	%	Chi-square/n	P-Value	Chi-square/n	P-Value
Gender		352	100.0	59	100.0	271	100.0				
	Male	178	50.6	31	52.5	148	54.6				
	Female	174	49.4	28	47.5	123	45.4	0.000192	0.77893	0.000254	0.77240
Race	White	315	89.5	47	79.7	247	91.1				
	Black	18	5.1	10	16.9	11	4.1	0.027598	0.00344	0.041148	0.00113 *
	Other	19	5.4	2	3.4	13	4.8				
		300	85.2	52	88.1	209	77.1	0.000846	0.55545	0.010770	0.05940
Diabetic	No	52	14.8	7	11.9	62	22.9				
	Yes	98	27.8	24	40.7	74	27.3	0.009707	0.04579	0.012574	0.04165
		254	72.2	35	59.3	197	72.7				
Hypertension	No	288	81.8	48	81.4	214	79.0				
	Yes	64	18.2	11	18.6	57	21.0	0.000018	0.93220	0.000512	0.68096
		289	82.1	46	78.0	219	80.8	0.001396	0.44885	0.000752	0.61844
Prior cataract extraction	No	63	17.9	13	22.0	52	19.2				
	Yes	324	92.0	55	93.2	270	99.6	0.000236	0.75528	0.040436	0.00026 *
		28	8.0	4	6.8	1	0.4				
Grid laser photocoagulation	No	63	17.9	10	16.9	33	12.2				
	Yes	288	81.8	48	81.4	238	87.8	0.000042	0.89631	0.003278	0.29905
	Missing	1	0.3	1	1.7	0	0.0				
Cystoid spaces - size	Absent	63	17.9	10	16.9	33	12.2				
	Small <= 200 um	80	22.7	12	20.3	34	12.5				
	Medium <=400 um	148	42.0	29	49.2	109	40.2	0.003875	0.66279	0.037796	0.00603
	Large > 400 um	60	17.0	7	11.9	95	35.1				
	Missing	1	0.3	1	1.7	0	0.0				
		237	67.3	41	69.5	152	56.1	0.000597	0.62430	0.012220	0.04799
SSR (Subretinal fluid)	No	108	30.7	16	27.1	111	41.0				
	Yes										

Total	BRVO		HRVO		CRVO		BRVO versus HRVO		CRVO versus HRVO	
	N	%	N	%	N	%	Chi-square/n	P-Value	Chi-square/n	P-Value
	7	2.0	2	3.4	8	3.0				
>5 DA in capillary non-perfusion	Missing									
	215	61.1	38	64.4	193	71.2	0.002715	0.37160	0.025140	0.01424
	37	10.5	4	6.8	4	1.5				
	100	28.4	17	28.8	74	27.3				

* Statistically significant after Hochberg adjustment

HRVO=hemiretinal vein occlusion; BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion; DA=disc area

Table 3: HRVO Study Eyes Compared with BRVO and CRVO Study Eyes: Baseline Demographics for Continuous Variables

Characteristic	Disease			BRVO versus HRVO		CRVO versus HRVO		
	BRVO	HRVO	CRVO	KS Statistic: D	P-value	KS Statistic: D	P-Value	
Baseline age (years)	N	352	59	271				
	Mean	66.4	69.7	67.5	0.0809	0.112702	0.5696	
	SD	11.2	10.6	12.4				
Disease duration (months)	N	352	59	271				
	Mean	4.5	4.1	4.3	0.051714	0.058728	0.9962	
	SD	3.9	3.6	3.7				
E-ETDRS visual acuity letter score at screening	N	352	59	271				
	Mean	57.7	52.6	51.4	0.206760	0.114641	0.5474	
	SD	12.3	14.4	14.0				
Center point thickness (microns)	N	349.0	59.0	268.0				
	Mean	519.6	559.8	659.2	0.218833	0.196813	0.0472	
	SD	186.1	182.4	228.3				
Total macular volume (mm ³)	N	218	35	173				
	Mean	9.8	10.0	10.5	0.155046	0.157721	0.4638	
	SD	1.8	1.6	2.0				
Disc areas of retinal thickening (photographs)	N	340	55	259				
	Mean	7.2	9.5	12.3	0.499733	0.596841	<.0001 *	
	SD	2.8	2.2	4.8				
Disc areas of retinal hemorrhage (photographs)	N	341	56	265				
	Mean	2.8	3.8	3.4	0.219522	0.205391	0.0405	
	SD	2.4	2.5	3.3				
Disc areas of leakage in the grid (FA)	N	343	58	258				
	Mean	5.8	8.2	10.9	0.546044	0.568030	<.0001 *	
	SD	2.3	1.8	5.0				
Disc areas of capillary non-perfusion (FA)	N	252	42	197				
	Mean	2.6	1.8	0.4	0.178571	0.122069	0.6807	

Characteristic	Disease			BRVO versus HRVO		CRVO versus HRVO	
	BRVO	HRVO	CRVO	KS Statistic: D	P-value	KS Statistic: D	P-Value
	6.5	5.2	1.7				
	SD						

* Statistically significant after Hochberg adjustment

HRVO=hemiretinal vein occlusion; BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion; KS= Kolmogorov-Smirnov; SD=standard deviation; E-ETDRS= Electronic Early Treatment of Diabetic Retinopathy Study; FA=fluorescein angiogram

Table 4:

Visual Acuity Letter Score Through 12 Months for Standard Care*: BRVO Study Eyes versus HRVO Study Eyes

Visit	BRVO						HRVO			
	N	Absolute		Change from Baseline		N	Absolute		Change from Baseline	
		Mean	Std	Mean	Std		Mean	Std	Mean	Std
Baseline	114	58.1	12.2	-	-	23	50.0	14.7	-	-
Month 4	105	58.8	18.8	0.7	15.3	22	51.5	21.0	0.7	13.6
Month 8	103	59.0	20.5	1.3	17.5	21	54.0	24.3	21	3.1
Month 12	100	62.1	18.9	3.8	16.7	21	57.4	23.6	21	6.3

* P=0.96 from statistical test for mean change in visual acuity letter score over 12 months between the SC groups

BRVO=branch retinal vein occlusion; HRVO=hemiretinal vein occlusion

Table 5:

Visual Acuity Letter Score Through 12 Months for Injection Groups*: BRVO Study Eyes versus HRVO Study Eyes versus CRVO Study Eyes

Visit	BRVO						HRVO						CRVO			
	N	Absolute		Change from Baseline		N	Absolute		Change from Baseline		N	Absolute		Change from Baseline		N
		Mean	Std	Mean	Std		Mean	Std	Mean	Std		Mean	Std	Mean	Std	
Baseline	238	57.4	12.4	-	-	36	54.2	14.1	-	-	183	51.0	14.5	-	-	-
Month 4	228	61.7	16.4	4.4	13.7	35	62.2	15.0	8.1	13.3	175	49.1	24.7	-1.9	21.1	21.1
Month 8	217	61.7	16.6	4.2	14.3	32	62.1	16.9	9.2	16.8	165	48.2	25.7	-2.7	22.6	22.6
Month 12	216	61.8	18.0	4.5	16.5	30	61.5	16.3	8.8	17.2	165	49.9	26.2	-1.4	23.3	23.3

* P<0.001 from statistical test comparing mean change in visual acuity letter score over 12 months the 3 disease areas; P=0.09 for BRVO versus HRVO; P<0.0001 for CRVO versus HRVO eyes

BRVO=branch retinal vein occlusion; HRVO=hemiretinal vein occlusion; CRVO=central retinal vein occlusion

OCT Center Point Thickness Through 12 Months for Standard Care^{*}: BRVO Study Eyes versus HRVO Study Eyes

Table 6:

Visit	BRVO					HRVO				
	N	Absolute		Change from Baseline		N	Absolute		Change from Baseline	
		Mean	Std	Mean	Std		Mean	Std	Mean	Std
Baseline	113	526	199	-	-	23	589	187	-	-
Month 4	104	375	178	-144	217	22	378	177	-222	215
Month 8	99	337	172	-186	248	21	294	143	-315	165
Month 12	99	285	162	-239	249	22	283	152	-317	202

^{*} P=0.60 from statistical test comparing mean change from baseline in center point thickness among two groups.

OCT=optical coherence tomography; BRVO=branch retinal vein occlusion; HRVO=hemiretinal vein occlusion

OCT Center Point Thickness Through 12 Months for Injection Groups* : BRVO Study Eyes versus HRVO Study Eyes versus CRVO Study Eyes

Table 7:

Visit	BRVO					HRVO					CRVO				
	N	Absolute		Change from Baseline		N	Absolute		Change from Baseline		N	Absolute		Change from Baseline	
		Mean	Std	Mean	Std		Mean	Std	Mean	Std		Mean	Std	Mean	Std
Baseline	236	517	180	-	-	36	541	180	-	-	181	642	236	-	
Month 4	222	396	193	-122	188	34	357	170	-184	208	169	497	284	-137	263
Month 8	208	376	180	-140	191	32	393	266	-159	261	153	457	267	-192	260
Month 12	203	342	177	-176	215	27	346	177	-189	180	154	409	258	-231	268

* P=0.20 from statistical test comparing mean change from baseline in center point thickness among 3 groups.

OCT=optical coherence tomography; BRVO=branch retinal vein occlusion; HRVO=hemiretinal vein occlusion; CRVO=central retinal vein occlusion

Table 8:

Intraocular Pressure and Cataract Adverse Events through 12 Months for Eyes in the Injection Arms

Characteristic	4 mg			1 mg		
	BRVO	HRVO	CRVO	BRVO	HRVO	CRVO
Eyes	118	20	91	120	16	92
% IOP > 10 mmHg above baseline	34%	50%	27%	8%	13%	16%
% IOP > 35 mmHg	10%	10%	9%	1%	6%	5%
% Initiation of IOP-lowering medication	42%	45%	35%	7%	19%	20%
Phakic eyes at baseline	95	15	76	97	13	77
Cataract progression	35%	33%	33%	24%	31%	26%
Cataract surgery	4%	0%	5%	0%	0%	0%

BRVO=branch retinal vein occlusion; HRVO=hemiretinal vein occlusion; CRVO=central retinal vein occlusion; IOP=intraocular pressure

Table 9:

Number of Grid Laser Photocoagulation Treatments in SC Groups: BRVO Study Eyes and HRVO Study Eyes

Number of Treatments Prior to 12 Months	All			No Dense Macular Hemorrhage at Baseline			Dense Macular Hemorrhage at Baseline		
	Mean	Lower 95 CI	Upper 95 CI	Mean	Lower 95 CI	Upper 95 CI	Mean	Lower 95 CI	Upper 95 CI
BRVO: n=114, 83, 31	1.48	1.30	1.66	1.80	1.61	1.98	0.65	0.35	0.94
HRVO n=23, 15, 8	1.65	1.23	2.08	1.93	1.40	2.47	1.13	0.43	1.82

SC=standard care; BRVO=branch retinal vein occlusion; HRVO=hemiretinal vein occlusion; CI=confidence interval

Table 10:

Number of Injections: BRVO, HRVO and CRVO: 1 mg and 4 mg

	1 mg			4 mg		
Number of Treatments < 12 Months	Mean	Lower 95 th CI	Upper 95 th CI	Mean	Lower 95 th CI	Upper 95 th CI
BRVO: n=120, 118	2.29	2.15	2.43	2.11	1.97	2.25
HRVO: n=16, 20	1.88	1.40	2.35	2.20	1.87	2.53
CRVO: n=92, 91	2.24	2.07	2.41	1.96	1.78	2.13

BRVO=branch retinal vein occlusion; HRVO=hemiretinal vein occlusion; CRVO=central retinal vein occlusion; CI=confidence interval