PROTOCOL

Treatment of Central Retinal Vein Occlusion Using STem Cells Study (TRUST)

(Phase I/II Randomized, Prospective, Double-masked, Sham-controlled Study of Intravitreal Autologous Bone Marrow CD34+ Stem Cell Therapy for Central Retinal Vein Occlusion)

IND#: 17023

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Study Funder: National Eye Institute (NEI)

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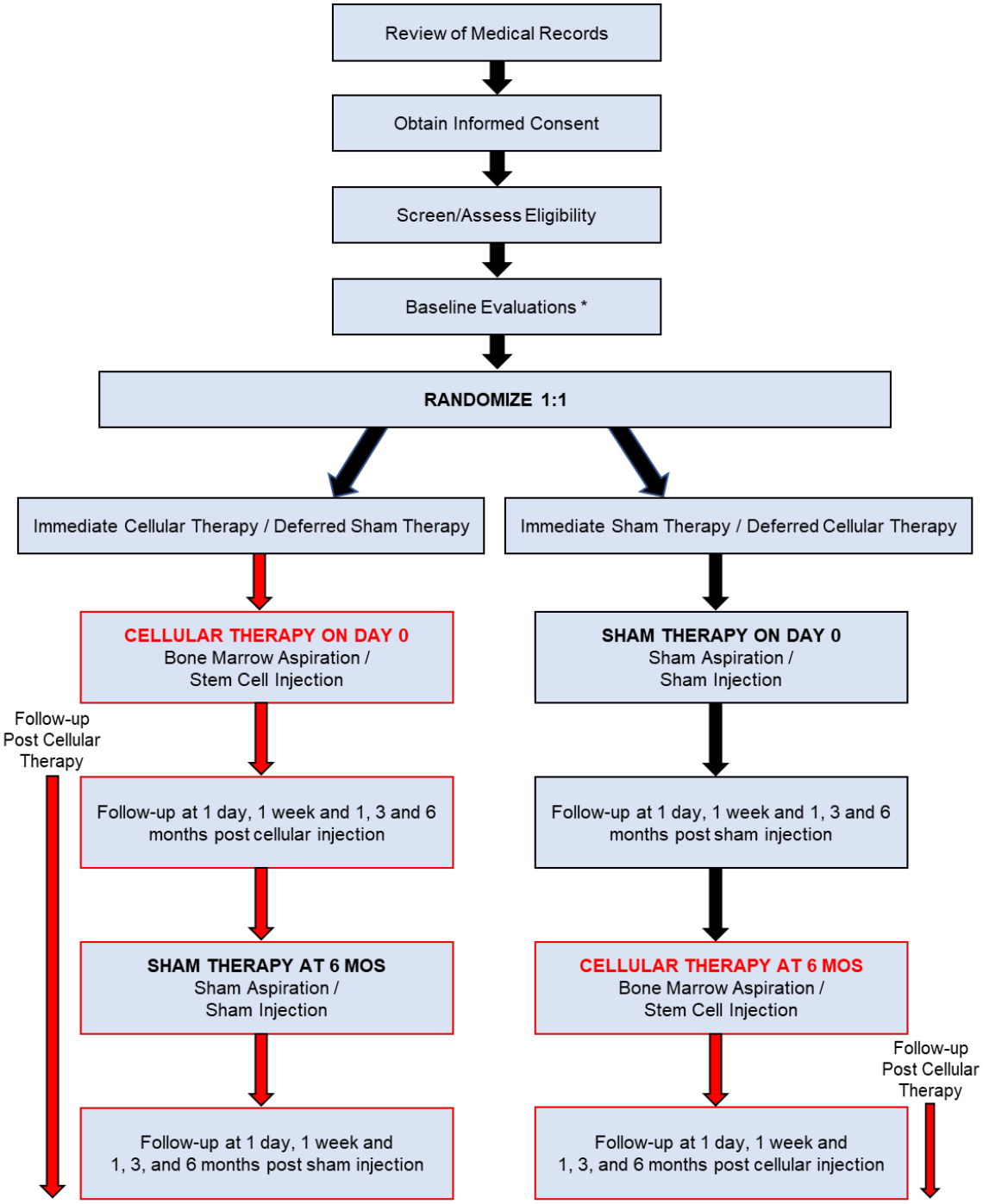
1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AF	Autofluorescence
AMD	Age-related Macular Degeneration
AREDS	Age-Related Eye Disease Study
BCVA	Best Corrected Visual Acuity
CBC	Complete Blood Count
CF	Counting Fingers
CNVM	Choroidal Neovascular Membrane
CRVO	Central Retinal Vein Occlusion
DCC	Data Coordinating Center
DSMC	Data and Safety Monitoring Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
EC	Enrollment Center
ERG	Electroretinography
ERM	Epiretinal Membrane
FA	Fluorescein Angiography
FDA	Food and Drug Administration
FP	Fundus Photography
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practices
GMP	Good Manufacturing Practice
IND	Investigational New Drug
IOP	Intraocular Pressure
NEI	National Eye Institute
MM	Medical Monitor
MOP	Manual of Procedures
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography Angiography
PI	Principal Investigator
ROS	Review of Systems
RPE	Retinal Pigment Epithelium
RVO	Retinal Vein Occlusion

Abbreviation	Definition
SAE	Serious Adverse Event
TRUST	Treatment of Central Retinal Vein Occlusion Using Stem Cells Study
UC	University of California
VEGF	Vascular Endothelial Growth Factor
VEGFR-2	VEGF receptor-2
VFQ	Visual Functioning Questionnaire

2.0 STUDY SCHEMA



*** Some baseline evaluations may be done post-randomization but prior to Day 0.**

3.0 STUDY SYNOPSIS

The goal of this phase I/II prospective, randomized, sham-controlled, double-masked clinical trial is to determine whether intravitreal autologous CD34+ stem cell therapy is safe, feasible and potentially beneficial in eyes with vision loss from central retinal vein occlusion (CRVO). Retinal Vein Occlusion (RVO) is a leading retinal vascular cause of vision loss in the elderly. CD34+ stem cells in human bone marrow are mobilized into the circulation in response to tissue ischemia for tissue revascularization and repair. Since local delivery of CD34+ stem cells benefits ischemic tissue, intravitreal delivery of CD34+ stem cells may benefit vision and retinal ischemia in eyes with RVO. A pilot clinical trial has shown no major safety or feasibility concerns using intravitreal autologous CD34+ bone marrow stem cells. In this proposed expanded phase I/II study, approximately 20 participants (20 eyes) with persistent vision loss from CRVO will be enrolled and followed for 1 year. Only eyes with CRVO will be enrolled to maintain uniformity in the study population. Total study duration will be approximately 60 months. This single-center study will be conducted at the University of California Davis (Enrollment Center). The Data Coordinating Center will be Emmes. The Study Chair/Principal Investigator will be Dr. Susanna Park. The study will be conducted under an IND cleared from the FDA. A Data and Safety Monitoring Committee (DSMC) will oversee the study. Participants will be randomized 1:1 to immediate cell therapy/deferred sham therapy or immediate sham therapy/deferred cell therapy, where deferred therapy refers to the therapy administered at month 6 and immediate therapy refers to therapy administered at baseline (either sham or cellular). At month 6, the (immediate) cell treated eye will receive sham treatment and the (immediate) sham treated eye will receive cellular therapy. The cell therapy involves a bone marrow aspiration, isolation of CD34+ cells from the aspirate under Good Manufacturing Practice (GMP) conditions, and intravitreal injection of the isolated CD34+ cells. The sham therapy involves a sham bone marrow aspiration with penetration of the skin but with no penetration of the bone and a sham injection without penetrating the eye. The participant, examining ophthalmologist, visual acuity examiner, photographers and OCT, perimetry, and ERG technicians will remain masked to study treatment assignment for study duration. A comprehensive eye examination with ETDRS best-corrected visual acuity, optical coherence tomography (OCT) and OCT angiography (OCTA), autofluorescence, fundus photography, fluorescein angiography, microperimetry, and electroretinography will be performed at baseline and serially. A subset of participants with good fixation on microperimetry and clear media on exam and commercial-grade OCTA and who give consent will have ultra-high resolution cellular retinal imaging using research-grade OCT and OCTA and adaptive optics-OCT at baseline. These participants with high quality images will have repeat imaging at 1 month after receipt of cellular treatment, with at least 2 of the participants randomized to the immediate sham therapy/deferred cellular therapy arm also having imaging 1 month after sham therapy. Post-release flow cytometry characterization will be performed to determine the composition of the CD34+ enriched final product in terms of hematopoietic versus angiogenic stem cells based on cell surface markers (i.e., CD133(+)/CD45(+)/CD34(+) vs CD31(+)/VEGFR-2(+)/CD45(-)/CD34(+)) provided there are an adequate number of cells, as determined by the GMP lab. The primary outcome measures for the safety and feasibility of the stem cell therapy will be the incidence and severity of ocular and systemic adverse events reported during Study Period 1 (i.e., the day of the first treatment (Treatment 1) up to but not including the day of the second treatment (Treatment 2)) and the mean and range of number of CD34+ cells isolated and the number injected into the eye. The secondary safety outcome measures are the incidence and severity of ocular and systemic adverse events reported throughout study duration. The secondary efficacy

outcome measures will be the changes in visual function, retinal perfusion and morphology following cell therapy. The long-term objective is to determine whether intravitreal autologous CD34+ cell therapy can minimize, or reverse vision loss associated with retinal ischemia without compromising safety.

4.0 BACKGROUND & SIGNIFICANCE

Bone marrow is one of the richest sources of adult stem cells.[1-3] These adult stem cells have been extensively studied and appear to play an important role in normal tissue repair and maintenance in the body.[4] Among these cells, CD34+ cells have been used clinically extensively for bone marrow transplantation and more recently explored in clinical trials as potential treatment for various ischemic conditions.[3-10]

Human CD34+ stem cells are often referred to as “hematopoietic stem cells” because they can be stimulated to differentiate into blood cells of various lineages. However, the multi-potency of the CD34+ cells extends beyond hematologic cell lines and the full regenerative capacity of these cells has yet to be explored.[1,5,8,11,12] In fact, the exact function of CD34 is not clear although it has been implicated to play a role in cell-cell interaction. Since endothelial progenitor cells, for instance, also express CD34 on their surface, a CD34+ population from bone marrow will include the revascularization population.[8,11,12] Since Asahara et al. described in 1997 the potential role of circulating CD34+ cells as endothelial precursor cells for tissue regeneration and angiogenesis following ischemia, clinical trials have explored the use of local intravenous infusion of autologous CD34+ cells from bone marrow as potential therapy for ischemia conditions such as cardiomyopathy and shown therapeutic benefit without safety issues.[4-9]

Hematopoietic stem cells, including human CD34+ cells, have the capacity to home into injured or damaged tissue, including ischemic tissue.[13-15] This property makes these cells different from embryonic and induced pluripotent stem cells. In animal models of retinal ischemia or retinal injury, CD34+ cells have been shown to home into the damaged retinal tissue when administered intravitreally.[16-18] Transretinal migration of these cells following intravitreal injection has been demonstrated in an animal model of retinal laser injury.[18] Long-term studies were conducted in NOD-SCID mice with acute retinal ischemia-reperfusion injury to determine the long-term effect of intravitreal injection of human CD34+ cells. This acute retinal ischemia model can be considered an animal model of retinal vein occlusion (RVO). Intravitreal injection of human CD34+ cells from bone marrow was well-tolerated long-term and the human cells were detected incorporated into the mouse retinal vasculature as long as 6 months following intravitreal injection with apparent normalization of the retinal vasculature and retinal morphology (Figure 1).[17] No long-term ocular or systemic safety issues were noted.

The regenerative effect of CD34+/hematopoietic stem cells from bone marrow extend beyond vascular repair. Intravitreal injection of autologous lineage-negative murine hematopoietic stem cells from bone marrow has been shown to slow down hereditary retinal degeneration in mice.[15] Since these cells were identified in the retinal vasculature and not the outer retina, a paracrine trophic regenerative effect on the photoreceptor was speculated. Our group has shown that intravitreal injection of human CD34+ cells from bone marrow in murine eyes with hereditary retinal degeneration and systemic immunosuppression results in rapid homing and integration of the human cells to the retinal surface layer.[19] Alterations in expression of over 300 genes in the murine retina were noted on microarray analysis. Pathways affected included those controlling apoptosis, photoreceptor maintenance and transduction. Again, the findings support a paracrine effect of intravitreal CD34+ cells on degenerating outer retina.

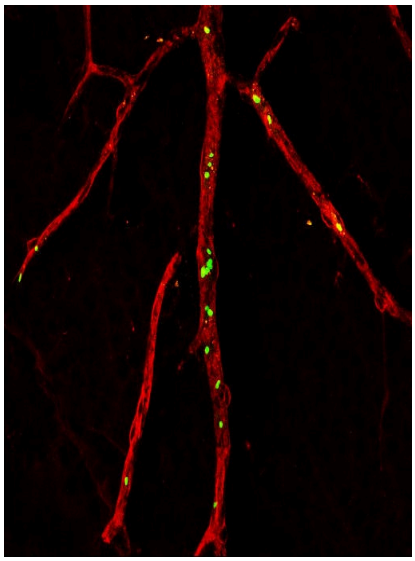


FIGURE 1: Long-term incorporation of human CD34+ stem cells in retinal vasculature after intravitreal injection. Immunohistochemical staining of the retinal vasculature of NOD-SCID mice 6 months after intravitreal administration of human CD34+ cells isolated from bone marrow in an eye with acute ischemia-reperfusion injury. The human cells (green) are identified incorporated into the mouse retinal vasculature which appears to have normalized.[17]

Based on these encouraging preclinical observations, two separate small clinical trials were conducted in Germany and Brazil exploring the use of intravitreal autologous bone marrow mononuclear cells as potential therapy for various ischemic or degenerative retinal conditions.[20,21] The mononuclear cell fraction of the bone marrow aspirate consists of a crude cellular mixture which contains mostly lymphocytes and monocytes and a low concentration of CD34+ cells (< 0.2%).[22] In both studies, intravitreal injection of these mononuclear cells was well tolerated and without adverse effects but minimal improvement in visual function was observed in treated eyes.

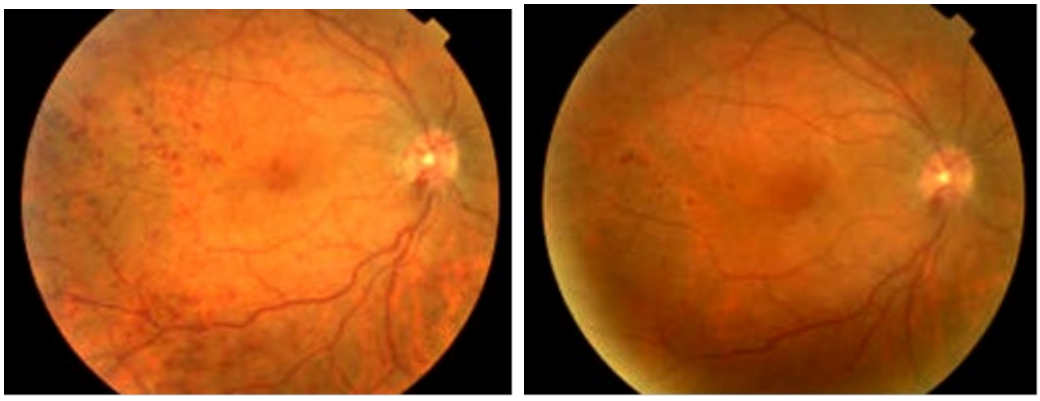


FIGURE 2: Fundus changes following intravitreal injection of autologous CD34+ stem cells in an eye with central retinal vascular occlusion. Fundus photography of an eye with persistent vision loss from a combined central retinal vein and artery occlusion 9 months earlier (left). Improvement in vision and fundus exam noted 3 months after intravitreal injection of autologous bone marrow CD34+ cells (right).[23]

By selecting out the CD34+ cells from bone marrow mononuclear cell fraction of the bone marrow aspirate, a higher concentration of these effector cells can be administered locally, potentially enhancing the therapeutic effect.[4-9] The study investigators have initiated a phase 1 study exploring the safety and feasibility of intravitreal injection of autologous CD34+ cells from bone marrow as potential treatment for ischemic or degenerative retinal conditions. This is based on an IND cleared by the Food and Drug Administration (FDA) and cross-referenced for the current IND (i.e., IND #13307). A total of 9 participants have enrolled in this study. The results of the first six participants who enrolled and completed the study have been published.[23] No ocular or systemic safety issues were noted in any enrolled participants during the six-month follow-up of the study and during the extended two-year follow-up as part of standard of care.[23] No feasibility issues were noted. The bone marrow aspiration was well tolerated under local anesthesia and a desired number of CD34+ cells could be obtained for intravitreal injection from a single bone marrow aspirate in each participant. Among the first six study eyes, the eye with retinal ischemia from a combined central retinal vein and artery occlusion appeared to have the most dramatic improvement in vision and fundus findings following intravitreal cell therapy (Figure 2).[23] Some improvement in the retinal microvascular abnormalities on fluorescein angiography and fundus photography could be observed within three months following the study treatment.

The rationale for using intravitreal autologous CD34+ cells from bone marrow for retinal regeneration following ischemic injury from RVO are the following: (1) there is a large unmet need given incidence of RVO. Retina vein occlusion is a leading vascular cause of vision loss in the elderly, second only to diabetic retinopathy. The incidence of RVO is 1 to 2% in 10 to 15 years among the population older than 40 years of age.[24-26] Approximately 16 million persons are afflicted with the condition worldwide.[26] The incidence of RVO increases with age and affects all ethnic and racial groups. The vision loss associated with RVO partially may be attributed to macular edema which can be treated with intravitreal drug therapy or laser photocoagulation.[27-29] However, even with resolution of macular edema, vision loss persists from macular ischemia and associated retinal degeneration. In fact, RVO is one of the leading causes of unilateral blindness in the elderly population.[24] In this study, only patients with CRVO will be enrolled for uniformity. (2) CD34+ cells include endothelial progenitor cells (EPCs) that play an important role in tissue and vascular repair from ischemia.[4] As such, clinical trials have been conducted showing efficacy of local administration of CD34+ cells isolated from bone marrow in ischemic conditions such as cardiomyopathy.[4-9] (3) Preclinical studies show that human CD34+ cells from bone marrow have ability to home and integrate into the damaged retinal vasculature long term following intravitreal administration without abnormal cellular proliferation or other adverse effects.[16,17] Since CD34+ cells can have both paracrine trophic effects and direct engraftment into the damaged retinal vasculature following intravitreal injection, these CD34+ cells can have regenerative effects on the retina and retinal vasculature via multiple mechanisms and at multiple levels.[17,22] (4) A pilot phase 1 clinical study conducted by investigators showed no major safety or feasibility issues associated with this cell therapy.[23] (5) Among the retinal conditions treated with this cell therapy in the pilot clinical trial, the participant with CRVO had the most dramatic functional and anatomic improvement following this cell therapy.[23] (6) Since RVO is typically acute and non-progressive, it is an ideal retinal ischemic model to study the regenerative potential of cell therapy in an early clinical trial.[30] Regenerative effects of cell therapy may be observed more readily in a non-progressive condition like RVO when compared to the chronic progressive condition such as diabetic retinopathy. The retinal vascular changes associated with RVO are clinically evident on

examination and on fluorescein angiography, unlike retinal vascular disorders such as retinal artery occlusion.

In this expanded phase I/II study, approximately 20 participants with persistent vision loss from CRVO with or without concurrent retinal artery occlusion will be enrolled and followed for one year to obtain safety and feasibility information regarding this stem cell therapy. The study has been designed as a randomized, prospective, double-masked sham-controlled study to obtain potential efficacy signals and trends. The study outcome will determine whether intravitreal autologous CD34+ cell therapy warrants further investigation as potential regenerative therapy for retinal disease.

5.0 OBJECTIVES

5.1 Primary Objective

The primary objective of the study is to assess the safety and feasibility of the stem cell therapy, which will be determined by the following outcome measures:

- Primary safety outcome: Incidence and severity of ocular and systemic adverse events reported during Study Period 1 (i.e., the day of the first treatment (Treatment 1) up to but not including the day of the second treatment (Treatment 2))
- Feasibility outcome: The mean and range of number of CD34+ cells isolated from the bone marrow aspirate and the number injected into the eye
- Secondary safety outcome: Incidence and severity of ocular and systemic adverse events reported throughout study duration

5.2 Secondary Objective

The secondary objective is to determine the effect of stem cell therapy on retinal function and morphology. Secondary efficacy outcomes include changes in best corrected visual acuity (BCVA), microperimetry, OCT/OCTA, electroretinography (ERG), fundus photography, fluorescein angiogram, autofluorescence, and quality of life.

5.3 Exploratory Objectives

Exploratory aims include descriptive analysis of changes in the retina and retinal vasculature at a cellular level using adaptive optics-OCT imaging, descriptive and quantitative analysis of changes in retinal vascular density and retinal morphology using ultrahigh resolution swept-source OCT and OCTA. An additional exploratory aim includes quantitative analysis of the hematopoietic and endothelial stem cell subcomponents and subcomponent of cells with VEGFR-2 in the harvested CD34+ cell population. A study survey will collect participants' experiences with various aspects of the study, including their impressions on timing of receipt of stem cell injection vs sham injection.

6.0 STUDY DESIGN

6.1 Description of Study

This is a phase I/II randomized, prospective, double-masked, sham-controlled study to determine the feasibility, safety and potential efficacy of intravitreal injection of autologous adult CD34+ stem cells from bone marrow (herein referred to as cellular therapy) in participants with vision loss from CRVO.

All potential participants diagnosed with CRVO will be screened by the PI or designee for study eligibility based on available clinical information. Those whose medical record suggests they may be eligible for the study will be asked to attend one or more screening visits at the UC Davis Eye Center. Informed consent will be obtained prior to conduct of any study procedures. Participants will undergo pre-treatment screening assessment and baseline testing to evaluate the extent of the condition and to confirm eligibility for the study. Once the participant is confirmed to be eligible, he/she will be randomized 1:1 to immediate cell therapy/deferred sham therapy or immediate sham therapy/deferred cell therapy.

Participants who are randomized to immediate cell therapy/deferred sham therapy will undergo a bone marrow aspiration followed by intravitreal injection of isolated CD34+ cells after baseline testing. Follow-up assessments will occur at 1 day, 1 week, 1 month, 3 months and 6 months post stem cell injection. Within 1 month of the 6-month follow-up study visit, participants will receive a sham bone marrow aspiration and sham injection. At least 1 day will separate the 6-month follow-up study visit and the sham therapy. Participants will continue to be followed at 1 day, 1 week, 1 month, 3 months and 6 months for a total follow-up of 12 months after the stem cell injection (and 6 months following the sham injection). For participants who did not complete the study satisfaction survey at the 12-month visit, an exit visit may occur following the 12-month visit to allow the survey to be completed.

Participants who are randomized to immediate sham therapy/deferred cell therapy will undergo a sham bone marrow aspiration followed by sham injection after baseline testing. Follow-up assessments will occur at 1 day, 1 week, 1 month, 3 months and 6 months post sham injection. Within 1 month of the 6-month follow-up study visit, participants will undergo a bone marrow aspiration followed by intravitreal injection of isolated CD34+ cells. At least 1 day will separate the 6-month follow-up study visit and the cellular therapy. Follow-up assessments will occur at 1 day, 1 week, 1 month, 3 months and 6 months thereafter for a total follow-up of 12 months after the sham injection (and 6 months following the stem cell injection). For participants who did not complete the study satisfaction survey at the 12-month visit, an exit visit may occur following the 12-month visit to allow the survey to be completed. The Study Schema is provided in Section 2.0.

6.1.1 Study Organization and Administration

This is a single-center clinical trial. The study organization consists of the following:

Study Funder: Under a cooperative agreement mechanism, The National Eye Institute (NEI) provides funding for the study. The NEI Program Officer has been in communication with the Study Chair/PI from study conception and had invaluable input in study design. In consultation with the investigative group, the NEI Program Officer appointed members of the Data and Safety Monitoring Committee (DSMC) to oversee the study.

Study Chair/Principal Investigator (PI): The Study Chair is also the PI for this single-center study. Dr. Susanna Park will function in this role. She conceived of this study and will take the administrative leadership for the study to ensure that the study progresses successfully and in a timely manner. She designed the study, wrote the Study Protocol and Manual of Procedures in conjunction with the Data Coordinating Center (DCC). She has submitted the regulatory documents to the FDA and obtained a new IND clearance for the proposed study (i.e., IND # 17023). She also submitted documents to the local IRB and has obtained study approval. She will work with the DCC to submit annual reports and any amendments recommended by the DSMC to the regulatory agencies. She will take a leadership role in study recruitment at the Enrollment Center (EC) and supervise the Clinical Trials Team at the Enrollment Center to ensure that the study is progressing according to the study protocol and in a timely manner. She will be responsible for ensuring that all adverse events (AEs) are entered into the study database and working in conjunction with the DCC to ensure those AEs meeting reporting requirements are indeed reported to the appropriate regulatory bodies in a timely manner. She will represent the study at the biannual meeting of the DSMC and take leadership in data analysis and manuscript preparation at study closeout.

Data Coordinating Center (DCC): The Data Coordinating Center (DCC, Emmes) will provide clinical trials management support throughout the course of the study, including in the following areas: data management; randomization; site activation; protocol monitoring including conduct of site initiation, interim and closeout visits; safety oversight; statistical leadership; data analysis and DSMC support. The DCC has been working with the Study Chair/PI on the study design and preparation of the Study Protocol and Manual of Procedures (MOP). The DCC will conduct a site visit before study initiation to verify that the study personnel at the Enrollment Center are adequately trained, to evaluate the facility and to ensure all required essential regulatory documents are approved. The DCC will work with the Study Chair/PI to finalize the data collection forms for the study before study initiation. The DCC will use a web-based electronic data capture (EDC) system for data collection and data management and will train the Study Coordinators at the Enrollment Center on the use of the EDC system. During the study, the DCC will be in regular communication with the Study Chair/PI to give updates on study progress. The DCC will continuously monitor safety information provided by the site throughout the course of the study. The DCC will organize and coordinate the biannual DSMC meetings and provide interim updates on study progress at these meetings. The DCC will conduct interim monitoring site visits throughout the course of the study, as well as conduct a study closeout visit. Final data analysis will also be the responsibility of the DCC, in collaboration with the Study Chair/PI.

Data and Safety Monitoring Committee (DSMC): Members of the DSMC are appointed by the NEI Program Officer in consultation with the investigative group. Members are selected for their relevant medical experience and expertise, knowledge of clinical trial methodology, and absence of conflicts of interest. The DSMC will meet prior to study initiation to review and approve the study protocol and informed consent. After study initiation, the DSMC will meet approximately every six months to review study progress until study closeout. These meetings will be organized by the DCC and attended by the NEI Program Officer, Study Chair/PI, DCC PI, Project Manager, and statistician, and members of the DSMC.

Enrollment Center (EC): For this single-center study, the Enrollment Center will be the University of California Davis Eye Center. The Study Chair, Dr. Susanna Park, will also be the PI of the Enrollment Center. She will be responsible for ensuring that all study personnel, including the

Study Coordinators, are knowledgeable about the study protocol and will work with the DCC to ensure all are properly trained in study procedures. She will also take the leadership role in submitting the regulatory documents to the local IRB and Stem Cell Oversight Committee, and the FDA. The UC Davis Eye Center Clinical Trials Team, under the supervision of the PI, will perform the baseline and follow-up study evaluations.

6.1.2 Study Masking Considerations

Given the nature of the study treatment and the study design in which participants are receiving both a stem cell injection and a sham injection, it is recognized that masking may be difficult to ensure. Nonetheless, efforts will be made to preserve masking as described below.

To maintain the masking for the study duration of each participant's follow-up period, there will be separate ophthalmologists designated for administration of study therapy and study visit follow-up examination after study therapy (**TABLE 1**). The PI will remain masked as the examining ophthalmologist for the study duration. The treating ophthalmologist will be an experienced retinal specialist and faculty member of the UC Davis Eye Center. He/she will remain unmasked to therapy assignment and perform the eye examinations during the first week of each participant's follow-up after sham or cellular therapy. An experienced retinal specialist from the Enrollment Center will be available as a backup unmasked treating ophthalmologist, and a separate experienced retinal specialist from the Enrollment Center will be available as a backup masked examining ophthalmologist. However, all efforts will be made to have the study therapy administered by the main treating ophthalmologist and all masked study examinations performed by the masked examining ophthalmologist (PI) to minimize confounding variables.

Study Coordinators from the UC Davis Eye Center Clinical Trials Team will be assigned to the study to manage the day-to-day activities regarding the study under the supervision of the PI, with the unmasked Study Coordinator being provided only general guidance from the masked PI. Study Coordinators will conduct study visits according to their masked or unmasked delegated assignment.

The masked and unmasked Study Coordinators will be responsible for scheduling all study visits taking utmost care to preserve the masking. Prior to randomizing the participant, the masked Coordinator will schedule the Treatment 1 and Treatment 2 study visits working under the pretense that both procedures involve stem cell therapy. Once the participant is randomized, the unmasked Study Coordinator will provide both the study hematologist and the GMP laboratory with information regarding which Treatment study visit will require bone marrow/cellular therapy and which will require sham aspiration/sham injection. The unmasked Study Coordinator will also schedule the post Treatment Day 1 and Week 1 study visits for both Study Periods.

The photographers and technicians obtaining OCT, perimetry and electroretinography (ERG) will be masked to the participants' treatment assignment to avoid bias in outcome assessment. The advanced retinal imaging team (described in Section 6.1.5), however, will be unmasked for the duration of the study.

At the time of informed consent and enrollment into the study and at the beginning of every study visit thereafter, participants will be reminded not to discuss details of the study procedures or their impressions of which injection they received with any member of the study team to preserve masking of the study team (i.e., investigators, technicians.)

TABLE 1: Enrollment Center Personnel – Masking for Randomized Treatment Assignment	
Study Roles	**Masked Status**
Principal Investigator	Masked
Examining Ophthalmologist	Masked
Masked Study Coordinator	Masked
Hematologist	Unmasked
Visual Acuity Examiner	Masked
Treating Ophthalmologist	Unmasked
Unmasked Study Coordinator	Unmasked
Photographers	Masked
OCT Technicians	Masked
Perimetry Technicians	Masked
ERG Technicians	Masked
Study Participants	Masked
Advanced Retinal Imaging Team	Unmasked
GMP Laboratory Team	Unmasked

The bone marrow aspiration and CD34+ cell isolation will be conducted by study co-investigators at the Enrollment Center. Certified hematologists who are faculty members of the UC Davis Cancer Center will perform the bone marrow aspiration or sham aspiration. Members of the Institute of Regenerative Cures leadership will oversee the CD34+ cell isolation from bone marrow aspirate in the Good Manufacturing Practice (GMP) laboratory. These co-investigators and contributors have a long-term working relationship with the PI and have participated in similar roles in the Phase 1 clinical trial for this cellular therapy. They are committed to this study.

6.1.3 Study Participant Demographics and Recruitment

Approximately twenty participants with history of persistent vision loss from CRVO in the study eye with or without concurrent retinal artery occlusion will be consented and enrolled if they meet study eligibility criteria. The vision loss must be persistent and over 6 months in duration as mandated by the FDA. The participants who meet the eligibility criteria will mostly be recruited from the clinic population of the Retina Clinic at the University of California Davis Eye Center and via referral from community ophthalmologists. There are at least four retinal specialists within the UC Davis Eye Center who can refer patients for the study. They are all investigators in the study. In addition, there are approximately fifteen community retinal specialists within the Sacramento, CA area who have expressed interest in referring patients for this study. They include retinal specialists in an HMO and a high-volume retina-only private practice. CRVO is a relatively common condition; thus, no major problem is anticipated in terms of availability of patients with CRVO. Although many of the patients seen in the Retina Clinic are patients undergoing treatment for macular edema or retinal neovascularization, these conditions often stabilize after treatment, but vision loss often persists. In eyes with severe macular ischemia, treatment of macular edema may be deferred if no visual benefit is anticipated with standard of care treatment.

Before study enrollment begins, the study will be registered on www.clinicaltrials.gov. Based on past experience of the PI, registering an actively enrolling clinical trial on this website results in direct self-referral of patients who might be interested in enrolling in the study. A recruitment letter will also be written and emailed to retinal specialists, general ophthalmologists, and optometrists in northern California. Patients and their providers from outside the Sacramento, CA region may contact the Enrollment Center directly via phone call or email to be considered for enrollment. These patients' medical records will be screened for eligibility by the study coordinator and PI. For patients living outside the Sacramento, CA area, enrollment preference will be given to patients residing within a five-hour driving distance of the Enrollment Center in Sacramento, CA in order to maximize study retention.

Gender and ethnicity are not exclusion criteria for the study since CRVO afflicts individuals of both genders and all ethnicities and races.[25] Thus, the anticipated ethnic distribution of the enrolled participants will likely reflect the ethnic/racial distribution of the clinic population at UC Davis Eye Center (**APPENDIX A**). The gender distribution will likely be equal among enrolled participants. No pregnant women will be enrolled since this is an experimental therapy with an unknown safety profile. Patients must be at least 18 years of age to enroll since they must be of age to sign the informed consent. The anticipated age distribution for this study enrollment will likely reflect the increasing prevalence of this condition from 1% to 5% as patients age from 40 years to 80 years of age.[24-26] Since there is more severe irreversible vision loss associated with RVO among patients > 60 years of age, the anticipated age distribution will be as follows:

> 60 years of age:	75%
40 to 60 years of age:	20%
18 to 40 years of age:	5%

6.1.4 Study Retention Strategies and Timeline

To maximize study retention during the 12-month follow-up period of the study, enrollment priority will be given to potential participants who are highly motivated to participate in the study. In addition, details of the study scheduled follow-up visits and tests will be reviewed with each potential participant before obtaining informed consent. Priority enrollment consideration will be given to potential participants living locally or within 5 hours driving distance of the Enrollment Center located in Sacramento, CA. In addition, enrollment priority will be given to potential participants who are of good general health and with good social and family support, as determined by the study staff based on interactions with the potential participant.

Once the patient is enrolled, both Study Coordinators and the PI will continually educate the participant on the nature of the study and the importance of continued follow-up and participation to minimize drop outs and missed visits. In addition, the Study Coordinators will contact the participants within a week of scheduled follow-up visits as a reminder of the appointment. This will be done by telephone or email. If a participant misses a study visit, he/she will be contacted promptly by the Study Coordinators to reschedule the visit within the time window allowed for that visit. Every effort will be made to maintain contact with the study participants even if the participant misses a scheduled study visit. The Study Coordinator involved in these appointment reminders and rescheduling will be either the masked or unmasked Study Coordinator depending on whether the study visit will be conducted by a masked or unmasked investigator.

All efforts will be made to make each study visit as efficient and pleasant as possible for the study participants. The masked and unmasked investigators and Study Coordinators will make every effort to address any issues or concerns regarding the study that may be raised by the participants and to develop a personal rapport with each of the study participants.

The anticipated timeline for the study is as follows:

Study Start-up:	12 months
Recruitment/Enrollment:	42 months
Follow-up:	12 months
Study Closeout:	6 months
Total duration of study:	72 months

Study Start-up (approximately 12 months):

Study start-up is anticipated to take approximately 12 months. This time period will be used to finalize the protocol, study documents, case report forms, and electronic data capture system; to form and hold the initial meeting of the DSMC and ensure all study personnel are trained in study procedures. The IND for the study was cleared by the FDA on July 7, 2016. The local IRB has previously approved the study protocol and informed consent form. Any changes to the study protocol and informed consent form recommended by the DSMC will be submitted to the FDA and local regulatory agencies (IRB and Stem Cell Oversight Committee) for final approval before study enrollment begins. The UC Davis Eye Center (Enrollment Center) clinical trial team has been involved in many multi-center clinical trials funded by NEI and has an excellent track record. In addition, the Enrollment Center is involved in the on-going phase I study of this cellular therapy and no hurdles or difficulties have been encountered implementing the study cellular therapy. Thus, the team is experienced in all aspects of this proposed study except the randomized treatment assignment, sham-control design, and masking procedures.

The DCC (Emmes) has contributed to the study design and the Manual of Procedures prior to study start-up. There has been continuous communication between the DCC and the Study Chair/PI and this communication will continue through study start-up and through the duration of the study.

Study Recruitment (approximately 42 months):

Recruitment is anticipated to take the 42 months. Note the FDA had initially mandated that enrollment be staggered by at least two weeks in the event that there is a safety issue observed associated with the study therapy. Although this mandate has been lifted recently in the cross-referenced IND based on available safety data of the pilot study, a conservative rate of enrollment is advised and planned. For the early part of enrollment for this phase I/II study (i.e., first 6 months of the enrollment period starting from the date the study was open to enrollment), enrollment will be staggered by at least 2 weeks.

An additional factor affecting rate of enrollment is the limited number of days the treatment can be administered. Available treatment days will be limited since the participant, the hematologist, the GMP facility, and the study treating ophthalmologist must all be available concurrently for study treatment to be administered. Furthermore, enrollment is anticipated to be slower than expected due to travel restrictions imposed by the COVID-19 pandemic that began during the study enrollment.

During the recruitment period, a biannual update on study enrollment and study retention rate will be presented to the DSMC by the DCC. Any study-related safety issues will also be presented. In addition, the Study Chair/PI will communicate at least monthly with the DCC regarding the recruitment schedule and study progress.

Study Follow-up (approximately 12 months):

Following the end of the study recruitment period, an additional 12 months will be required to allow all participants to complete the study. During this period, all efforts will be made by the masked investigators and Study Coordinator at the Enrollment Center to avoid early study dropout. Because participants remain masked to therapy assignment during the follow-up, it is anticipated that there will be minimal dropout during the first six months until all participants receive the second study therapy. At that point, all participants will have received the cellular therapy, and more likely that participants may consider dropping out of the study. The Enrollment Center team will make every effort to encourage the study participants to keep all follow-up study visits to ensure participants are adequately followed for safety following this experimental therapy and so that the study can gain information regarding the effects of the cellular therapy, whether they be potentially beneficial or adverse.

Study Closeout (approximately 6 months):

Once the last participant enrolled has terminated from the study, study closeout will begin. Study closeout is estimated to take approximately 6 months. During the study closeout period, the DCC protocol monitor will conduct a site closeout visit and once all data issues have been resolved, the database will be locked. Final data analysis will be conducted by the DCC and in conjunction with the PI and the DSMC. The final study manuscripts will be written and prepared for publication by the PI and study collaborators by the end of study closeout and submitted to peer-reviewed journals after review and approval by the DSMC and the DCC.

6.1.5 Study Procedures and Visit Schedule

TABLE 2 summarizes the study visit schedule and procedures for the participants enrolled in the two arms of the study. Each potential participant will be screened by the PI or designee for study eligibility prior to enrollment based on available clinical information. A written informed consent will be obtained after a detailed explanation of the tests, potential risks and benefits of the study therapy, the study randomization, and scheduled follow-up visits.

Each participant will undergo pre-therapy screening assessments and baseline testing to confirm the diagnosis and evaluate the extent of the condition. The screening tests include a comprehensive eye examination including ETDRS BCVA (best corrected visual acuity), fluorescein angiography, fundus photography, microperimetry, and optical coherence tomography (OCT)/OCT angiography. The screening tests will be performed within one month of first study therapy although results of any of these study procedures performed up to 45 days prior to first study therapy may be used to confirm diagnosis and determine eligibility for the study at the investigator's discretion if no change in visual function or eye examination is noted during the period. In addition, the medical and ophthalmic history and concomitant list of medications, if any, will be reviewed to ensure that the patient qualifies for the study based on the inclusion and exclusion criteria of the study. A blood sample to perform a CBC test will be obtained, and vital signs will be taken. If the patient is a woman of child-bearing potential, a urine pregnancy test will

be performed within 2 weeks prior to study treatment. Details regarding whether a participant is of childbearing potential is outlined in **APPENDIX B**.

Data on any participant who signs the informed consent but fails to meet all eligibility criteria based on the screening evaluation will be collected along with the reason(s) for not qualifying for the study.

TABLE 2: Study Visit Schedule

	Screening Period	Study Period 1						Study Period 2						Study Exit^^
Visit	**Screening/ Baseline 1**	**Study Treatment 1**	**Day 1**	**Week 1**	**Month 1**	**Month 3**	**Month 6/ Baseline 2 ***	**Study Treatment 2 ***	**Day 1**	**Week 1**	**Month 1**	**Month 3**	**Month 6**	
Target Month	+	-	-	-	1	3	6	-	-	-	7	9	12	^^
Target Day	-	0	1	7	28	91	181	182	183	190	210	273	364	^^
Window	+	-	-	±2 d	±7 d	±14 d	±30 d	±30 d	-	±2 d	±7 d	±14 d	±30 d	^^
Medical History/ROS	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ophthalmic History	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent	X													
Vital Signs	X	X[#]	X	X			X	X[#]	X	X				
CBC	X			X			X			X				
Urine Pregnancy Test**	X						X							
ETDRS VA	X	X[^]	X[^]	X[^]	X	X	X	X[^]	X[^]	X[^]	X	X	X	
Micro-Perimetry	X				X	X	X				X	X	X	
Eye Exam & IOP	X	X[@]	X	X	X	X	X	X[@]	X	X	X	X	X	
Fundus Photography	X					X	X					X	X	

TABLE 2: Study Visit Schedule

	Screening Period	Study Period 1						Study Period 2						Study Exit^^
Visit	**Screening/ Baseline 1**	**Study Treatment 1**	**Day 1**	**Week 1**	**Month 1**	**Month 3**	**Month 6/ Baseline 2 ***	**Study Treatment 2 ***	**Day 1**	**Week 1**	**Month 1**	**Month 3**	**Month 6**	
Target Month	+	-	-	-	1	3	6	-	-	-	7	9	12	^^
Target Day	-	0	1	7	28	91	181	182	183	190	210	273	364	^^
Window	+	-	-	±2 d	±7 d	±14 d	±30 d	±30 d	-	±2 d	±7 d	±14 d	±30 d	^^
FA	X					X	X					X	X	
OCT/OCTA	X				X	X	X				X	X	X	
Inclusion/ Exclusion Criteria	X													
Randomization	X													
AF	X					X	X					X	X	
ERG***	X				X	X	X				X	X	X	
NEI VFQ	X						X						X	
Advanced retinal imaging @@	X				X						X			
Hematology Consult	X						X							
Cellular or Sham Therapy##		X						X						
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment Pause Guideline Review			X	X	X	X	X	X	X	X	X	X	X	

TABLE 2: Study Visit Schedule

	Screening Period	Study Period 1						Study Period 2						Study Exit^^
Visit	**Screening/ Baseline 1**	**Study Treatment 1**	**Day 1**	**Week 1**	**Month 1**	**Month 3**	**Month 6/ Baseline 2 ***	**Study Treatment 2 ***	**Day 1**	**Week 1**	**Month 1**	**Month 3**	**Month 6**	
Target Month	+	-	-	-	1	3	6	-	-	-	7	9	12	^^
Target Day	-	0	1	7	28	91	181	182	183	190	210	273	364	^^
Window	+	-	-	±2 d	±7 d	±14 d	±30 d	±30 d	-	±2 d	±7 d	±14 d	±30 d	^^
Post Procedure Satisfaction Survey				X						X				
Study Satisfaction Survey													X	X

Abbreviations: AF—fundus autofluorescence; CBC—complete blood count; FA—fluorescein angiography; IOP—intraocular pressure; OCT/OCTA—optical coherence tomography and angiography; VA—visual acuity; ROS—review of systems.

Shaded cells represent visits which are conducted by unmasked staff.

+Screening assessments may be done in one or more visits within 1 month of study treatment at Day 0 although results from within 45 days prior to study treatment at Day 0 may be considered at the discretion of the investigator.

*The Baseline 2 visit and the Study Treatment 2 visit must be separated by at least one day but no more than 30 days.

#Vital signs at Study Treatment 1 and Study Treatment 2 will be performed just before and after bone marrow or sham aspiration.

For females of child-bearing potential (see **APPENDIX B for definition), urine pregnancy testing should be done within 2 weeks prior to sham or cellular therapy.

^Using refraction previously obtained at Baseline visit.

@Study Treatment 1 and Study Treatment 2 eye examinations will be done before and after sham or cellular therapy.

***Includes full field and multifocal ERG.

@@ Includes research-grade ultra-high-resolution OCT and OCTA and adaptive optics-OCT in select patients who sign a separate consent. Advanced retinal imaging will be done on a separate day than the standard OCT/OCTA due to the time required for imaging. Imaging will be performed at baseline and participants with high quality images will have repeat imaging at 1 month after stem cell treatment, with at least 2 of the participants randomized to the deferred cellular therapy arm also having imaging after sham therapy. The images will be acquired and processed by unmasked investigators. Images will be masked prior to their review by a masked investigator and groups of images will be reviewed together to preserve masking.

For Immediate Cell Therapy/Deferred Sham Therapy group, study treatment at Day 0 consists of bone marrow aspiration followed by intravitreal injection of CD34+ cells, and study treatment at 6 months consists of sham bone marrow aspiration followed by sham injection. For Immediate Sham Therapy/Deferred Cell Therapy group, treatment at Day 0 consists of sham bone marrow aspiration followed by sham injection, and study treatment at 6 months consists of bone marrow aspiration followed by intravitreal injection of CD34+ cells.

^^ The incorporation of the Exit Visit results from changes made to protocol v8.0 where follow-up was shortened to one year. For those participants who completed the Month 12 visit prior to the approval of protocol v8, they will complete the Exit Visit within 30 days of the approval of protocol v8.0. The Exit Visit is comprised of review and close-out of AEs and concomitant medication records, and completion of the study satisfaction survey.

Once the participant qualifies for the study, the participant will be randomized 1:1 to either of the following study treatments: immediate cell therapy/deferred sham therapy or immediate sham therapy/deferred cellular therapy, where cell therapy consists of bone marrow aspiration and intravitreal injection of isolated CD34+ cells and sham therapy consists of sham bone marrow aspiration and sham injection. Immediate therapy refers to procedure administered at baseline while deferred therapy refers to procedure administered at month 6 of the study. The following assessments will be completed prior to study treatment that occurs on Day 0 and may be performed before or after randomization depending on the clinic or participant scheduling needs: autofluorescence, full field and multifocal electroretinography (ERG) and quality of life questionnaire. Additional imaging using a research-grade ultra-high-resolution OCT/OCTA and adaptive optics-OCT instruments will also be performed on a select subgroup of participants who qualify and consent.

Prior to randomization, the participant will meet with the study hematologist to review the aspiration procedure. The hematologist will review the participant's medical history, concomitant medications and blood work (including CBC) to ensure that the participant is a good candidate for a bone marrow aspiration. Any abnormal lab work and review of systems will be reviewed by the hematologist to determine whether it would impact the outcome of the bone marrow aspiration procedure and continued enrollment in the study.

Using the DCC's electronic data capture (EDC) system, Advantage eClinical®, the unmasked Study Coordinator will randomize the participant, and will disseminate this information in a confidential manner to the hematologist and GMP laboratory as described in section 6.1.2.

On the morning of the study procedure, the participant will meet with the hematologist and the unmasked study coordinator to ensure there are no new contraindications to proceeding with study treatment that day.

The aspiration procedure will generally be performed in the minor procedure room at University of California Davis Eye Center or at the University of California Davis Alpha Stem Cell Clinic after premedication with oral medications to minimize anxiety and pain. Local anesthesia will be given at the site of the planned aspiration. Just before the aspiration procedure, there will be a surgical timeout to confirm the participant's identity, participant's (study) ID, and procedure to be performed.

The bone marrow aspiration consists of an Illinois needle inserted into the iliac crest region. Approximately 10 to 50 ml of bone marrow aspirate will be obtained from the iliac crest per participant after no more than four separate bone punctures. After the bone marrow is obtained, the site of the insertion will be cleaned and bandaged, and the participant will be instructed regarding care of the puncture site. The marrow will be placed in heparinized tubes and transported promptly to the GMP laboratory of the Institute for Regenerative Cures.

For the sham aspiration, an Illinois needle will be attached to a syringe and will be used to penetrate the skin in the iliac crest region to simulate the skin changes following bone marrow aspiration. The bone, however, will not be penetrated. After the needle is withdrawn, the site of the insertion will be cleaned and bandaged, and the participant will be instructed regarding care of the puncture site.

For the cellular therapy portion, GMP-grade CD34+ BMSCs will be isolated using a Ficoll column to isolate the mononuclear cell fraction and the Miltenyi CliniMACS system will be used to isolate

the CD34+ cells from the mononuclear cell fraction. There will be no genetic research testing performed. The isolated CD34+ cells will be washed, subjected to stat sterility assays (including endotoxin assay and gram stain), and stat viability testing with trypan blue staining and resuspended in 0.15 cc volume of BSS Plus. The final stem cell product (0.1 cc containing at least 800,000 viable nucleated CD34+ cells (where the cell count is based on the Miltenyi CliniMACS cell sorting process as noted above) will be sent to the Eye Center in a 1 ml tuberculin syringe for intravitreal injection. The remaining 0.05 cc of the final stem cell product will be used for post-release analysis to characterize the final stem cell product. This will include flow cytometry for CD34 and CD3 content and 7-AAD viability testing. Additional analysis for potency and characterization of the final product will be performed. These additional analyses will include flow cytometric panel analysis for hematopoietic stem cells that are CD133(+)/CD45(+)/CD34(+) versus angiogenic cells (i.e., endothelial progenitor cells) that are CD31(+)/VEGFR-2(+)/CD45(-)/CD34(+). In addition, the post release flow cytometry panel will include analysis of CD34+ cells with VEGF receptor-2 (VEGFR-2), namely VEGFR-2+/CD34+, as well as, % CD133(+); % CD31(+); % CD45(+); % VEGFR-2 (+).

On the morning of the study procedure, ETDRS VA is performed prior to the aspiration procedure and study injection. In addition, the unmasked treating ophthalmologist will perform a complete eye exam including fundus examination and a slit lamp examination of the study eye to ensure there are no new changes from baseline. This is done prior to study injection. The isolated CD34+ cells will be injected intravitreally by the unmasked treating ophthalmologist (retinal specialist) under local anesthesia. The intravitreal injection will be performed within two hours and on the same day following release of the final stem cell product from the GMP laboratory.

Just before intravitreal injection or sham injection, there will be a surgical timeout to confirm the participant's identity, participant's (study) ID, procedure to be performed and the eye in which the injection will be performed. Once the study eye is confirmed, the eye will be gently massaged for 5 minutes to soften the eye. The study eye will be anesthetized with topical proparacaine eye drops. Additional anesthesia at the discretion of the treating ophthalmologist will consist of either a cotton-tipped applicator soaked with 4% lidocaine or lidocaine gel applied 2 to 5 minutes over the injection site or administration of 2% lidocaine subconjunctival injection over the injection site using a sterile 30g needle. Povidone-iodine (5%) will be instilled in the fornix and the injection site and the participant will be asked to blink once to evenly coat the surface of the eye with povidone-iodine. A sterile lid speculum will be placed to keep the eyelid open during the procedure. A cotton-tipped applicator soaked in 5% povidone-iodine will be applied to the conjunctiva directly over the intended injection site. The povidine-iodine is allowed to dry for 30 to 60 seconds. Or, IF THE PATIENT IS ALLERGIC TO IODINE, one drop of topical antibiotic (zymar) will be applied every 5 minutes for 3 doses prior to injection. Then, a sterile eyelid speculum will be placed to keep the eyelids open during the procedure.

For the intravitreal injection, the isolated cells (suspended in sterile saline volume of 0.1 cc) will be injected into vitreous through the pars planar (i.e., 4mm behind the limbus) using a 30-gauge needle. For the sham injection, an empty uncapped tuberculin syringe will be placed with gentle pressure at the injection site to simulate intravitreal injection (i.e., nothing will be injected into the eye) after applying conjunctival lidocaine with a cotton-tipped applicator.

After stem cell injection or sham injection, the lid speculum will be removed, and the participant's vision will be measured to make sure it is at least counting fingers (CF). Indirect ophthalmoscopy

will be performed to ensure that the central retinal artery is perfused and to ensure that there are no complications associated with the injection. Intraocular pressure (IOP) will be measured after injection. If the vision is hand motions or light perception and IOP is > 40 mm Hg, glaucoma medications will be started to lower IOP. If the vision is no light perception and IOP is > 40 mm Hg, a paracentesis will be performed after reapplying 2 to 3 drops of 5% povidine-iodine solution and opening the eyelid with a sterile lid speculum. A 30g needle attached to a 1 mL syringe will be used to remove a maximum of 1 mL of aqueous from the anterior chamber. The lid speculum will be removed and visual acuity of at least counting fingers will be confirmed. Indirect ophthalmoscopy will be performed to confirm perfusion of the central retinal artery.

Following stem cell injection or sham injection, a complete eye examination will be performed to ensure there is no new change after the injection. This will include a slit lamp examination which will check for hyphema or cells visible in the anterior vitreous. Then, the eye will be washed with balanced saline solution, followed by application of antibiotic eye drop and erythromycin or similar antibiotic eye ointment. Then, the eye examination chair will be reclined to allow the participant to be in the supine position for 30 minutes. Thereafter, the participant will be discharged and instructed to use topical antibiotic drops four times a day in the injected eye for one week. The number of viable nucleated CD34+ cells to be injected per eye will be recorded and will range from 800,000 to 10 million, depending on the yield of the bone marrow aspiration and the isolation procedure and where the cell count is based on the Miltenyi CliniMACS cell sorting process. The percent viability of the cells as noted pre-release using trypan blue staining by the GMP laboratory will also be recorded. Any irregularity in size or shape of the cells in the final product as noted by the GMP laboratory staff will also be recorded.

The participants will have a complete eye examination 1 day and 1 week (±2 days) after their first study treatment (either cell or sham) by the unmasked treating ophthalmologist. Thereafter, a follow-up examination 1 month (±7 days), 3 months (±14 days) and 6 months (±30 days) will be conducted by the masked examining ophthalmologist. At month 6, the participant will receive the second study treatment (either cellular or sham therapy which is the opposite of what they originally received) by the unmasked treating ophthalmologist. Prior to the receipt of the second study treatment, the participant will meet with the study hematologist to review the aspiration procedure. Similar to the first consult, the hematologist will review the participant's medical history, concomitant medications, and blood work (including CBC) to ensure that the participant is still a good candidate for bone marrow aspiration. Any abnormal lab work and review of systems will be reviewed by the hematologist to determine whether it would impact the outcome of the bone marrow aspiration procedure and continued treatment in the study. In addition, females of child-bearing potential must have a negative pregnancy test within 2 weeks of the second study treatment. Similar to what occurs for the first treatment, the study team will meet with the participant on the morning of the study procedure to ensure there are no new contraindications to proceeding with study treatment that day.

Following the study injection, the unmasked treating ophthalmologist will conduct a follow-up exam 1 day and 1 week after this second study treatment. The masked examining ophthalmologist will conduct an exam 1 month, 3 months (±14 days) and 6 months (±30 days) after the second study treatment (i.e., at approximately 7, 9 and 12 months after the first study treatment).

The bone marrow aspiration wound site will be inspected visually for infection at the 1 day and 1 week (±2 days) post-procedure examinations by the unmasked treating ophthalmologist.

Fundus photography, fluorescein angiography, and autofluorescence will be performed at screening/baseline and at 3 months (±14 days) and 6 months (±30 days) after each treatment, and as needed at the discretion of the investigator to assess any significant change upon clinical examination. Commercial-grade OCT/OCT angiography, microperimetry and ERG will be performed at screening/baseline and at 1 month (±7 days), 3 months (±14 days) and 6 months (±30 days) after each treatment, or as needed at the discretion of the investigator to assess any significant change in retinal function and perfusion. The NEI VFQ questionnaire will be completed at screening/baseline and at 6 months following each study treatment. A study feedback questionnaire will be administered at 1 week after each study treatment and at study exit.

Select participants, who at screening have stable fixation on microperimetry and clear media (study eye) defined as Optovue OCTA signal strength of 6 or greater using the 3mm macular scan, will be invited to participate in an optional sub-study. The sub-study involves ultra-high-resolution OCT/OCTA and adaptive optics-OCT imaging. Imaging will be performed at baseline and participants with high quality images will have repeat imaging at 1 month after receipt of stem cell therapy. Approximately 2 of the participants randomized to immediate sham therapy/deferred cellular therapy will also have imaging done 1 month after receipt of sham therapy. Thus, the Advanced Retinal Imaging team will be unmasked investigators for the study duration. Since this is a time-consuming procedure, it may be scheduled on a separate date from other procedures requiring fixation, such as perimetry or ERG. The processed images will be evaluated for qualitative abnormalities by a masked investigator in bulk at a later date. The quantitative assessment of the images, e.g., retinal thickness and vascular density, will be assessed by the unmasked Advanced Retinal Imaging team after completion of image processing.

The schedule of assessments is presented in **TABLE 2**.

6.1.6 Study and Data Monitoring

During the course of the study, the PI and the DCC will work in conjunction with the DSMC to ensure that the trial is conducted properly and in accordance with the study protocol. Before study initiation, the DCC will organize the initial meeting of the DSMC to allow the committee members to review, offer advice, and approve the study protocol, informed consent form, and other supporting study documents. During this meeting, the overall plan for safety monitoring and procedures and guidelines for reporting adverse events will be reviewed and approved by the DSMC. In addition, the overall plan for statistical analysis and monitoring the study for early stopping and/or pausing enrollment will be discussed. Thereafter, the DSMC will meet on an approximate biannual basis. The DCC will produce data tables and conduct analyses as appropriate for review by the DSMC.

Protocol monitoring will be a continuous process performed both at the DCC and at the Enrollment Center. The DCC staff will be in regular communication with both Study Coordinators and the PI, via email or teleconference, at least monthly to discuss general study issues and to assure the site is up to date with data completion. At least monthly, data quality reviews will be conducted to assess level of missing data, review requests for missing values and missing forms exceptions, and run data checks for missing and inconsistent data. Any departure from procedures or requirements outlined in the protocol will be classified as protocol deviations.

Prior to study initiation, a site initiation visit will be conducted by a DCC protocol monitor to ensure the site possesses adequate facilities and staffing to conduct the study, that site personnel have sufficient knowledge to ensure the study is conducted in accordance with GCP, applicable regulations, and the approved protocol, and that they are adequately trained in study policies and procedures. Interim monitoring visits will be conducted to monitor for informed consent documentation, protocol adherence, reporting of protocol deviations, study outcomes, participant safety, maintenance of appropriate source documentation and regulatory reviews. Protocol monitoring visits conducted by a DCC monitor will occur approximately every 6 months after enrollment begins. A site close-out visit will be conducted at the conclusion of the study. Complete and accurate regulatory documentation, complete data entry, and no pending action items are required before the site is closed out.

6.2 Rationale for Study Design

Human CD34+ cells in bone marrow are mobilized into the circulation in response to tissue ischemia and play an important role in tissue revascularization.[4,22] By injecting the isolated CD34+ cells from bone marrow directly into the vitreous cavity, the regenerative potential of these cells may be maximized to treat retinal ischemia. Animal studies have shown that intravitreally injected human CD34+ cells home into sites of retinal injury and ischemia and may play a role in revascularization. This has been demonstrated in animal models of diabetic retinopathy, acute retinal ischemia-reperfusion injury and retinal laser injury,[13-19] Thus, we hypothesize that these CD34+ cells may help cells in the retina recover from ischemia and regain visual function. RVO is the condition to be studied since it is the second most common retinal vascular cause of vision loss. With RVO the retinal ischemic event is usually acute, rather than chronic and progressive as noted in diabetic retinopathy, potentially allowing therapeutic effect of cellular therapy to be appreciated more readily. Since this is primarily an early phase safety and feasibility study, we will only enroll individuals with severe persistent vision loss from CRVO despite standard of care treatment with laser, surgery or intravitreal anti-vascular endothelial growth factor (VEGF) or corticosteroid therapy, if eligible (refer to Section 7.1.2 Inclusion/Exclusion Criteria). CRVO was selected to maintain uniformity in the study eye. It is of note that at least six participants with vision loss from various ischemic and degenerative retinal conditions have already been treated with this cellular therapy as part of a phase I study, and no safety or feasibility issues were noted during the 6 to 24 month follow-up.[23] Among the study eyes, the eye with vision loss from a combined CRVO and retinal artery occlusion appeared to have the greatest improvement by visual acuity, ERG, fluorescein angiography and microperimetry following this cellular therapy. The improvement was noted as early as one month following cell injection and sustained during the six-month follow-up period of the study. This proposed expanded phase I/II study is planned to further explore the effect of intravitreal autologous CD34+ cells in eyes with persistent vision loss from CRVO. By conducting a larger study of CRVO with longer follow-up, more feasibility and safety information can be obtained regarding this therapy. By comparing retinal functional and anatomic changes following study treatment to sham treatment, some efficacy information can also be obtained. Autologous CD34+ cells will be used to avoid cell rejection issues. These CD34+ cells will be harvested from bone marrow, one of the richest sources for these cells.[1-3] Although CD34+ cells mobilized into the circulation have been used for bone marrow transplantation, these mobilized cells may not completely share the characteristics of CD34+ cells in bone marrow.

The study is a randomized prospective study in which participants and all study personnel participating in eye examinations and outcome assessment will remain masked for the study duration of 12 months. Only the advanced retinal imaging team, treating ophthalmologist, the hematologist conducting bone marrow aspiration, and the study coordinator conducting these treatment and immediate post-treatment examination visits will be unmasked. All participants will remain masked for the study duration. The study design allows all participants to receive cellular therapy by month 6. The rationale for this study design is based on the expectation that participants receiving intravitreal cell injection would likely note a beneficial effect of cellular therapy, if any, by month 3 based on the observations of the preliminary phase I study.[22]

The proposed clinical trial is supported by preclinical observations. Human CD34+ cells from bone marrow have been shown to be multi-potent and observed to home into ischemic retinal blood vessels and damaged retinal cells very quickly following intravitreal injection in animal models.[15-19] These human cells could be detected in mouse retinal vasculature as long as 6 months following intravitreal injection in a murine model of acute retinal ischemia-reperfusion with apparent normalization of the retinal vasculature.[17] No long-term safety issues were noted locally or systemically in the murine study. Of note, the number of CD34+ cells injected into the murine eyes in these preclinical safety studies is equivalent to about 10 million CD34+ cells injected in human eyes if adjusted for differences in eye size and volume. Thus, the upper limit of number of viable nucleated CD34+ cells to be injected intravitreal for this phase I/II study will be 10 million, where the cell count is based on the Miltenyi CliniMACS cell sorting process.

6.3 Outcome Measures

6.3.1 Primary Safety and Feasibility Outcome Measures

The primary outcome measures for the safety and feasibility of the stem cell therapy are the following:

- Incidence and severity of ocular and systemic adverse events reported during Study Period 1 (i.e., the day of the first treatment (Treatment 1) up to but not including the day of the second treatment (Treatment 2)
- The mean and range of number of CD34+ cells isolated from the bone marrow aspirate and the number injected into the eye

6.3.2 Secondary Outcome Measures

The secondary safety outcome measures are the incidence and severity of ocular and systemic adverse events reported throughout study duration.

The secondary efficacy outcome measures for the study will be used to describe the effect of therapy on retinal function and morphology as outlined in **TABLE 3**.

TABLE 3: Secondary Efficacy Outcome Measures	
Modality	**Outcome Measure**
Visual Acuity	ETDRS Visual Acuity Letter Score
Microperimetry	% Reduced Sensitivity
	Average Threshold
OCT	Macular Thickness by ETDRS zone
	Macular Volume
	Average Macular Thickness
	Presence of CME
	Presence of Subretinal Fluid
	Integrity of Photoreceptor Layer (IS/OS Junction)
	Integrity of Photoreceptor Layer (ELM)
	Presence and number of hyper-reflective foci in vitreous, intraretinal and subretinal
	Length of longest DRIL in line scans
	Presence of ERM
	Presence of VMT/VMA
OCTA	Foveal avascular zone size
	Automated Superficial and Deep Vascular Density (VD) by ETDRS zone
	VD Analysis of Superficial plexus and deep plexus
	RNFL Thickness
	Whole image capillary density %
	Inside disc capillary density %
	Retinal peripapillary capillary density %
Multifocal ERG	Number of abnormal amplitude hexagons
	Mean amplitude S.D.
	Number of abnormal latency hexagons
	Mean Latency S.D.
Full-field ERG	% normal amplitude for a-wave and b-wave under scotopic conditions
	% normal latency for a-wave and b-wave under scotopic conditions
	% normal amplitude for a-wave and b-wave under photopic conditions
	% normal latency for a-wave and b-wave under photopic conditions
	% of normal Flicker amplitude and latency
	% normal amplitude for Dark adapted 3.0 ERG + OP a-wave and b-wave under scotopic conditions
	% normal latency of Dark adapted 3.0 ERG + OP a-wave and b-wave under scotopic conditions
Autofluorescence (AF)	Area of decreased autofluorescence
	Area of increased autofluorescence

TABLE 3: Secondary Efficacy Outcome Measures	
Modality	**Outcome Measure**
Fundus Photography	Degree of retinal hemorrhages by ETDRS/Networc zones
	Degree of pigment changes by ETDRS/Networc zones
	Degree of retinal fibrosis by ETDRS/Networc zones
	Degree of NV by ETDRS/Networc zones
	Degree of pre-retinal hemorrhage by ETDRS/Networc zones
Fluorescein Angiogram (FA)	Foveal avascular zone integrity
	Area of non-perfusion within ETDRS Grid
	Area of non-perfusion within Networc Grid
	Grade of capillary non-perfusion
	Number of microaneurysms
	Grade of telangiesctatic vascular changes
Quality of Life	Mean total score
	Mean subscale scores

6.3.3 Exploratory Outcome Measures

Exploratory outcome measures include:

- Changes in the retina and retinal vasculature at a cellular level as visualized using Adaptive optics-OCT instrument in the study eye at 1 month following each treatment.
- Changes in the retinal vascular density and retinal morphology using ultrahigh resolution swept-source OCT and OCTA in the study eye at 1 month following each treatment.
- Characterization of the hematopoietic and endothelial stem cell subcomponents and subcomponent of cells with VEGFR-2 in the harvested CD34+ cell population.
- Number of participants who were able to correctly identify the timing of receipt of sham and cellular therapies.

6.4 Safety Plan

To ensure safety of participants and integrity of data in this trial, the following data and safety monitoring plan will be followed during the study:

1. The site investigators will continuously monitor participant safety and be responsible for reporting adverse events and serious adverse events (SAEs) from the Enrollment Center to the DCC Medical Monitor (MM) through Advantage eClinical, the electronic data capture system developed and maintained by the DCC. In order to maintain masking, the unmasked treating ophthalmologist will review any AE or SAE noted within 14 days following study treatments and determine severity and possible relationship to study treatment or procedure. He/she will report these adverse events to the Medical Monitor as noted above. Any AE or SAE noted later than 14 days after study treatments will be reviewed by the masked investigator (usually PI) who will review the events for severity and possible relationship to study therapy or procedure. The AE or SAE will be reported to the MM as noted above. To maintain masking as much as possible, for SAEs

determined by the MM to be related to study treatment and unexpected, the MM will share the SAE narrative with the PI. The reporting to the IRB of record will be done in a masked fashion as “Cellular Therapy/Sham Therapy”. The investigator who originally reported the adverse event will be responsible for determining relationship to therapy and severity and following events through resolution.

2. The site Principal Investigator is required to review all unanticipated problems involving risk to participants or others, serious adverse events, and all participant deaths associated with the protocol and provide an unbiased written report of the event.
3. The DCC Medical Monitor will continuously monitor safety information provided by the site throughout the trial. All SAEs will be reviewed at the time they are reported. The DCC Medical Monitor will communicate the reporting of the SAE via email to the PI, the NEI Project Officer and the DSMC after review and confirmation of SAE has been completed. The Medical Monitor will also indicate whether he/she concurs with the details of the report provided by the site investigator. Reviews will be conducted in Advantage eClinical and will be a part of the safety database. All adverse events will be reviewed on a weekly basis to observe trends or unusual events. If any concerning safety patterns are noted, this information will be conveyed to the PI for further discussion. During these discussions, masking will be preserved as much as possible unless safety considerations dictate otherwise.
4. Data and Safety Monitoring Committee (DSMC): An independent DSMC will review participant data biannually, or on a schedule otherwise requested by the DSMC, to monitor for the occurrence of any unexpected risks or futility of treatment during the course of the study. The DSMC will convene and operate based on a pre-established charter created prior to the initiation of the trial. The DSMC will be permitted to seek additional independent expertise, as needed. The DSMC will provide safety oversight of the trial, monitor the progress of the study, and recommend continuation or modification of the trial, as appropriate. A summary of the review, including the recommendation to continue or modify the study, will be distributed to the site for submission to the local regulatory agencies.

This study will be conducted under an IND that has been cleared by the FDA because the study explores the safety of an experimental treatment for treating retinal disease. Thus, the study will comply with the adverse events definitions and reporting requirements for clinical trials established by the FDA and as outlined in Section 8.0 of the study protocol.

There were no observed adverse effects of intravitreal injection of human CD34+ cells from bone marrow in animal models.[17] In addition, there were no systemic or ocular adverse events noted among the participants that have already been treated with intravitreal autologous CD34+ bone marrow stem cells under the cross-referenced IND for this study treatment.[23] Nonetheless, in order to minimize the risk of intraocular infection (i.e., endophthalmitis) or any other adverse effects that may be associated with intravitreal injection or cell therapy, the following precautions will be taken:

- The fluid obtained from washing the cells after CD34+ cell isolation will be cultured for 14 days.
- Gram stain and endotoxin measurement of the fluid obtained from washing the isolated cells will be performed stat and before the cells are released for intravitreal injection.

- The study eye will be cleansed with 5% betadine and sterile lid speculum will be used to open the eyelid before intravitreal injection is performed. Antibiotic drops will be used after the injection for one week.
- The injected participants will be examined one day, one week and one month after injection to look for evidence of endophthalmitis or other side effects of the injection. The 1 day and 1-week evaluation will be done by the unmasked treating ophthalmologist. The 1-month evaluation will be conducted by the masked ophthalmologist (usually PI). Intravitreal injection of drug is routinely done in the eye clinic under topical anesthesia with minimal risk of side effects from the injection. Endophthalmitis incidence has been reported to be < 1% per injection and usually diagnosed during the first week after injection.[29] Retinal tear and detachment, bleeding, cataract, and transient glaucoma are also potential side-effects of the injection but occur much less frequently. If these new conditions occur within 1 month of study procedure, they may be related to study treatment. Otherwise, it will be assumed unlikely to be related to study treatment. If any of these conditions occur, the participant will be promptly treated based on what is considered standard of care.
- Enrollment will be staggered by at least two weeks during the first 6 months of the enrollment period starting from the date the study is open to enrollment in case any adverse event associated with the study treatment is observed. Thereafter, enrollment may be slightly accelerated to maintain study timeline.

In addition, the following pause guidelines have been established. If any of the following events occur, enrollment will be paused, and the data reviewed by the DSMC.

1. Development of any new intraocular tumor in the injected eye during the study period in any participant.
2. Endophthalmitis or Severe Inflammation resulting in > 3 lines of vision loss attributable to the study therapy in any participant, i.e., final culture of cell isolate shows organism despite negative immediate release tests, or this AE is noted in two or more participants despite negative final culture and immediate release tests.
3. Loss of vision of > 3 lines not attributed to normal progression of the eye condition, noted in two or more participants during the study period. The DSMC will be notified at the time that one participant has loss of vision of > 3 lines, but a pause would not be triggered until a second participant experiences the event.
4. New retinal vascular event in the study eye during the study period noted in two or more participants not attributable to normal progression of the underlying eye condition during the study period.
5. Development of ocular neovascularization in the study eye not attributable to normal progression of the underlying eye condition during the study period in two or more participants.
6. Development of new sustained elevation in intraocular pressure above 30 mmHg not controlled with medical therapy and/or paracentesis and directly attributed to the studied therapy in any participant.

7. Any adverse event leading to enucleation or loss of the eye directly related to study therapy.

These guidelines may be further refined by the DSMC before initiation of the study. In the event any of these pause guidelines are triggered during the course of the study, both the IRB and FDA will be notified within 7 days and the study enrollment will be paused until further notice from the FDA and/or IRB. The study participant will be followed and treated according to standard of care until condition stabilizes or resolves.

6.5 Compliance with Laws and Regulations

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCP), and the Institutional Review Board and Stem Cell Oversight Committee of the University of California Davis Medical Center.

7.0 MATERIALS AND METHODS

7.1 Participants

7.1.1 Participant Selection

All participants will be enrolled at the Retina Clinic at the University of California Davis Eye Center. The participants may include patients already being treated in the clinic and patients referred to the Enrollment Center for consideration for study enrollment. All patients with persistent vision loss from CRVO will be considered for enrollment if they meet the eligibility criteria.

7.1.2 Inclusion/Exclusion Criteria

7.1.2.1 Study Eye Inclusion/Exclusion Criteria

Inclusion criteria for the study eye are:

1. Clinical diagnosis of central retinal vein occlusion (CRVO) confirmed by review of medical records and screening assessment.
2. BCVA obtained during the screening period is in the range of 20/40+ to 20/400- (ETDRS letter score in the range of 18 to 73, inclusive).
3. Duration of vision loss from CRVO $\geq$ 6 months to $\leq$ 42 months.

Exclusion criteria for the study eye are:

1. Previous eye treatment with intravitreal or periocular steroids, laser or intraocular surgery within 6 months prior to enrollment (i.e., date ICF signed) or treatment is expected to be given during the study period.
2. For eyes requiring treatment to prevent recurrent macular edema, on-going intravitreal anti-VEGF treatment is expected to be given at an interval < every 8 weeks during the study period or anti-VEGF therapy was started less than 24 weeks prior to informed consent.
3. History or concurrent ocular herpes infection.
4. Active non-herpetic eye infection diagnosed within 8 weeks from enrollment (i.e., date ICF signed).
5. Glaucoma requiring treatment with more than 2 medications, laser or intraocular surgery.
6. Active uveitis or history of recurrent uveitis or uveitis involving the posterior segment.
7. Presence of cataract that is impairing vision.
8. Presence of lens or lens implant subluxation.
9. History of ocular trauma that is currently impairing vision.
10. Any concurrent optic nerve or retinal disease that is visually significant or likely to progress to visual significance during the 1-year study follow-up. The excluded eyes include eyes with AREDS category 2 to 3 age-related macular degeneration (AMD) with foveal involvement of drusen or RPE changes, and any AREDS category 4 AMD eyes. For eyes with ERM, the excluded eyes include eyes with OCT evidence of foveal deformation. For optic nerve disease, eyes with any associated visual field deficit or history of associated

CNVM are excluded. For glaucoma eyes, eyes requiring glaucoma laser trabeculectomy or glaucoma surgery to maintain IOP are excluded.

11. Active retinal or iris neovascularization.
12. Macular edema requiring on-going therapy or where such treatment is expected during the study period, with the exception of anti-VEGF treatment given at an interval of 8 weeks or greater.
13. Significant media opacity precluding view of the fundus for examination, photography or optical coherence tomography (OCT) including cataract and vitreous haze.
14. High myopia (≥ 9 diopters)
15. Amblyopia
16. Other cause contributing to vision loss at screening.
17. History of any of the following procedures: corneal transplant, glaucoma surgery, or intraocular silicone oil.

7.1.2.2 Participant-Level Inclusion/Exclusion Criteria

Participants must meet the following inclusion criteria:

1. Age ≥ 18 years of age.
2. Female participants of child-bearing potential (see **APPENDIX B** for definition) must not be pregnant or breastfeeding and have a negative urine pregnancy test within 14 days prior to sham injection and/or CD34+ cell injection.
3. Females of childbearing potential must have had a hysterectomy, be completely abstinent from intercourse or must agree to practice effective contraception for the duration of the study. Acceptable methods of contraception include hormonal contraception, intrauterine device, barrier methods (diaphragm, condom) with spermicide, or surgical sterilization (tubal ligation).
4. Able and willing to sign informed consent.
5. Able to keep follow-up appointments for at least 12 months as determined by the investigator.

Participants with any of the following criteria will be excluded from the study:

1. Concurrent treatment with an investigational drug or device.
2. Concurrent use of systemic immunosuppressive therapy or history of use within 3 months prior to enrollment (i.e., date ICF signed).
3. Concurrent use of anticoagulation therapy except for aspirin without an acceptable safe stopping plan for study treatments.
4. Known history of coagulopathy or other hematologic abnormality that may put participant at risk for bleeding or infection or raise concerns about quality or quantity of CD34+ cells isolated.
5. History of allergy to fluorescein dye.

6. Participant who has had a prior or concomitant malignancy with the exception of the following: 1) adequately treated basal or squamous cell carcinoma of the skin, or 2) any other malignancy from which the patient has remained disease free for more than five years.
7. Current active systemic infection as evidenced by fever greater than 100.4 or any evidence of systemic infection as determined by the study physician.
8. Any diagnosis of active infection or vaccination within 8 weeks prior to receipt of study treatment.
9. Diabetes mellitus with known systemic complications by self-report or physician-determined by medical history or examination.
10. History of prior radiotherapy to head/neck area.
11. Poorly controlled hypertension with systolic > 180 or diastolic > 95.
12. Serious medical or psychiatric condition that, in the opinion of the Investigator, would make study participation hazardous to the participant or compromise study findings or would prevent the participant from completing the study.
13. Any physical characteristic that precludes ability to perform study diagnostic testing.

7.1.2.3 Selection of Study Eye

If both eyes meet all of the study eye eligibility criteria outlined in section 7.1.2.1, the study eye will be the one with the worse visual acuity as noted at the screening visit. If visual acuity is the same, then the eye with stable fixation on microperimetry will be selected as the study eye. If both eyes have stable fixation, then the eye with lower macular sensitivity will be the study eye.

7.2 Method of Treatment Assignment

This is a randomized, prospective, double-masked, sham-controlled study. Eligible participants will be randomized in a 1:1 ratio, using a computerized block randomization scheme, to immediate cellular therapy/deferred sham therapy or immediate sham therapy/deferred cellular therapy, where cellular therapy consists of bone marrow aspiration and intravitreal injection of isolated CD34+ cells and sham therapy consists of sham aspiration and sham injection.

Randomization will occur after informed consent has been obtained and once a participant is confirmed to be eligible. Great care will be taken to choose participants who are highly motivated to participate so as to prevent drop-out post-randomization.

7.3 Study Treatment

Bone marrow aspiration, CD34+ stem cell isolation and intravitreal administration will be performed using sterile techniques. All three procedures will be done on the same day to maximize viability of the isolated cells. Similarly, the corresponding sham bone marrow aspiration and sham injection will be administered within the same day. The number of viable nucleated CD34+ cells to be injected in the eye will vary from 800,000 to 10 million cells per eye, depending on the volume of the marrow aspirated and the efficiency of the stem cell isolation procedure, where the cell count is based on the Miltenyi CliniMACS cell sorting process. On average, we anticipate injecting about one million CD34+ stem cells per eye in a volume of 0.1 ml.[23]

7.4 Concomitant and Excluded Therapies

All participants will be treated with topical antibiotics in the study eye for one week after the intravitreal injection (including eyes with sham injection) to minimize the risk of infection. During the course of the study, no other intraocular injection (with the exception of maintenance anti-VEGF therapy as described below), retinal laser or surgeries will be administered in the study eye unless the participant develops a new ocular condition that requires therapy as part of standard of care. An adverse event form will be completed in Advantage eClinical to report the occurrence of any new ocular condition requiring intervention. The report will include specification of the intervention taken for the new condition. (See section 8.6.) In addition, a concomitant medications form will be completed to provide information about all medications/interventions the participant takes/receives. If the study eye develops macular edema which would need to be treated with intravitreal anti-VEGF therapy as standard of care, intravitreal anti-VEGF therapy will be administered but will not be administered 4 weeks before or after either study procedures. New macular edema with Central Macular thickness of > 300 microns with concurrent decrease in BCVA of 2 or more lines will be used as criteria for initiating intravitreal anti-VEGF therapy as part of standard of care. Among patients who have been maintained on intravitreal anti-VEGF therapy as standard of care prior to study enrollment at an interval of 8 weeks or greater, intravitreal anti-VEGF therapy will be continued as part of standard of care but not administered 4 weeks before or after study procedures. All elective eye surgeries or procedures will be deferred until the end of the study if possible. Participants may receive vaccinations (e.g., seasonal flu, COVID-19); except within 8 weeks prior to receipt of any study treatment (Treatment 1 and 2).

7.5 Study Assessments and Monitoring of Study Progress

All participants will be examined 1 day, 1 week (±2 days), 1 month (±7 days), 3 months (±14 days), and 6 months (±30 days) following each of the two therapies (sham or cellular). These examinations will evaluate for any ocular adverse effect associated with the therapy and to gauge for any possible benefit. The details of the diagnostic tests to be performed are as outlined in **TABLE 2** for the 2 study groups. Participants will follow the same follow-up schedule regardless of which study group they are assigned.

During the first week after cellular therapy, the bone marrow aspiration site will be visually inspected for evidence of infection or bleeding. To maintain masking, a similar post-procedure examination will be performed for the participants receiving sham therapy.

The study progress will be monitored by the Study Chair/PI and the DCC. After every six months or on a schedule approved by the DSMC, a summary of study enrollment, study retention, adverse events, and study outcomes as appropriate will be presented and reviewed by the DSMC. An annual report of the study progress will be submitted to the local regulatory agencies and the FDA.

7.6 Participant Discontinuation/Replacement

Participants have a right to withdraw from the study at any time and for any reason. The Enrollment Center may request to withdraw a participant because of protocol deviation, administrative reasons, safety concerns, inadequate number of viable nucleated CD34+ cells harvested for intravitreal injection (where the cell count is based on the Miltenyi CliniMACS cell sorting process) or any other valid and ethical reasons. A study termination form will be completed citing the reason for the termination. In the event that a participant is terminated from the study

after randomization and prior to receipt of treatment (cellular or sham) at the Treatment 1 visit regardless of the reason, an additional participant will be accrued as a replacement. In the event that a participant receives the first treatment but opts not to receive the second treatment, an additional participant will be accrued as a replacement, but the original participant will be encouraged to return for all study visits to ensure the participant's safety is not compromised. The replacement participant will receive both treatments and will be followed for 12 months, the same as any other participant enrolled in the study. If a participant is terminated or withdraws from the study following the receipt of the second treatment, the participant will again be encouraged to return for all study visits for safety monitoring but will not be replaced. A maximum of one participant may be replaced, regardless of timing of withdrawal. If a participant terminates the study due to having less than 800,000 viable nucleated CD34+ cells (where the cell count is based on the Miltenyi CliniMACS cell sorting process) in the final product for intravitreal injection, the participant will have the option to receive the harvested cells as part of the on-going open-label pilot study provided that the harvested cells pass the release criteria for quality and sterility.

7.7 Study Discontinuation

This study may be terminated by the Study Chair/PI, Enrollment Center, FDA, the local regulatory agencies or NEI at any time. The DSMC may also recommend termination. Reasons for terminating the study may include the following:

1. The incidence and severity of adverse events in this or other studies indicates a potential health hazard to participants
2. Participant enrollment is unsatisfactory
3. Data recording is inaccurate or incomplete

7.8 Statistical Methods

7.8.1 General Design

This is a phase I/II randomized, prospective, double-masked, sham-controlled study to determine the feasibility, safety and potential efficacy of intravitreal injection of autologous adult CD34+ cells from bone marrow in participants with vision loss from CRVO. Participants will be randomized 1:1 to immediate cellular therapy/deferred sham therapy or immediate sham therapy/deferred cellular therapy. After their first treatment (cellular or sham), participants will be followed for 6 months, at which time participants who initially received sham treatment will receive cellular treatment and vice versa.

7.8.1.1 Outcomes

The primary outcome measures for the safety and feasibility of the stem cell therapy are incidence and severity of ocular and systemic adverse events reported during Study Period 1 (i.e., the day of the first treatment (Treatment 1) up to but not including the day of the second treatment (Treatment 2)), and the mean and range of number of CD34+ cells isolated from the bone marrow aspirate and the number injected into the eye. All adverse events reported throughout the study duration will also be examined as the secondary safety outcome measure.

The secondary efficacy outcome measures will be used to describe the effect of therapy on retinal function and morphology in the study eye. They include visual acuity letter score based on the ETDRS chart, macular sensitivity from microperimetry, OCT parameters including macular thickness and macular volume, OCT angiography parameters including foveal avascular zone

size and vascular density, parameters from multifocal ERGs including macular signal amplitude and latency and number of abnormal amplitude and latency hexagons, parameters from full-field ERG including measurements of the “a” and “b” wave amplitudes and latency under scotopic and photopic conditions and flicker amplitude, area of decreased and increased autofluorescence, foveal avascular zone integrity and percent of the retina with capillary non-perfusion on fluorescein angiography, degree of retinal hemorrhages, pigment changes, retinal fibrosis, NV and pre-retinal hemorrhage on fundus photography, and total score and subscale scores on vision-related quality of life as measured on the NEI VFQ-25. Each will be examined at baseline, and serially following each treatment. See Section 6.3.2 for a complete list of planned outcome measures.

Exploratory outcomes include descriptive analysis of changes in the retina and retinal vasculature at a cellular level as visualized using Adaptive optics-OCT instrument following cellular therapy and sham therapy, changes in the retinal vascular density and retinal morphology using ultrahigh resolution swept-source OCT and OCTA following cellular therapy and sham therapy, and characterization of the hematopoietic and endothelial stem cell subcomponents and subcomponent of cells with VEGFR-2 in the CD34+ cell population. We will also characterize participants' experience with various aspects of the study, including their impressions on timing of receipt of cellular therapy vs sham therapy, through the use of participant surveys. The latter is to determine if masking was maintained among participants during the study. We will report on the number of participants who were able to correctly identify the timing of receipt of the sham and cellular therapies.

7.8.2 Analysis of Primary and Secondary Outcomes

7.8.2.1 Safety and Feasibility

Any ocular or systemic adverse events (AEs) from all participants will be utilized to summarize safety data for this phase I/II study. All reported AEs will be analyzed and subdivided into pre-treatment and post-treatment AEs, where post-treatment is defined as those occurring on or after the day of the first treatment (cellular or sham). AEs will be summarized by presenting the number of events, and also by counts and frequencies for the number of participants with AEs, and the severity and relatedness of each AE to study treatment (i.e., CD34+ cells) or study procedure (i.e., intravitreal injection). Events related to bone marrow or sham aspiration will also be presented. Detailed listings of post-treatment AEs and pre-treatment AEs will be provided. All AEs will be coded using MedDRA® dictionary version 21.0 or higher. A similar approach will be taken to the presentation of Serious Adverse Events (SAEs).

Time trends in the occurrence of adverse events are also of interest. The primary safety outcome will be assessed at month 6 (at the end of Study Period 1). Adverse events that occur during the Study Period 1 will be broken down by whether the AE occurred following the sham or cellular treatment to assess differences in the adverse event experience between the two treatment arms. In addition, in order to assess whether there are any trends in when adverse events are reported from time of cellular therapy, we will also present adverse events based on how much time has elapsed from receipt of cellular therapy. Depending on how many events are reported, we may create categories for reporting purposes (e.g., events reported between Day 0 and 1-month post-therapy, events reported between 1 and 6 months, events reported between 6 and 12 months, etc.). In this analysis, data will be collapsed over both treatment arms.

To assess feasibility, the number and percent of study participants undergoing successful bone marrow aspiration will be summarized. The mean and range of volume of bone marrow aspirate, number of CD34+ cells isolated and number of CD34+ cells injected intravitreally will be described.

7.8.2.2 Efficacy

All secondary outcome analyses will follow a similar form and strategy as outlined in the SAP. Data from the study eye will be presented. Tables and graphs of each outcome and change from baseline in each outcome will accompany the results of the analyses as appropriate and will be used to visualize the trends over time. See Section 6.3.2 for a list of outcomes of interest. A (modified) intent-to-treat approach will be followed in which all participants who were randomized *and received the first injection* (cellular or sham) will be included in the analysis and analyzed in the arm to which they were randomized.

The primary analysis will be a comparison at 6 months between those who receive immediate cellular therapy vs those who receive immediate sham therapy. A t-test will be used for continuous outcomes and Fisher's exact test or an appropriate non-parametric test may be used for categorical outcomes. Comparisons at other time points prior to 6 months may also be performed.

An additional analysis will look at treatment effect duration for those who receive immediate cellular therapy and assess whether the treatment effect remains the same at 6 and 12 months or increases/decreases as time passes.

As noted in Section 6.3.2, there are many outcomes of interest within each modality. P-values calculated from the statistical tests noted above will only be used as an indication of strength of association and should not be used for hypothesis testing.

7.8.2.3 Exploratory Endpoints

The following exploratory analyses will be performed:

- Analysis of changes in retina and retinal vasculature at a cellular level as visualized using Adaptive optics-OCT instrument in the study eye at 1 month following each treatment.
- Analysis of changes from baseline in retinal vascular density and retinal morphology ultrahigh resolution swept-source OCT and OCTA at 1 month following each treatment.
- Analysis correlating percent hematopoietic and endothelial stem cell subcomponents and percent of cells with VEGFR-2 in the CD34+ cell population with primary and secondary outcome measures.
- Descriptive analysis of number of participants who were able to correctly identify the timing of receipt of sham and cellular therapies.

7.8.3 Sample Size Considerations

There is no formal sample size calculation for this small phase I/II study. A sample size of 20 participants was chosen to ensure that it is financially feasible to conduct the study and logistically possible to complete the study enrollment within the study period. The primary objective is to assess the safety and feasibility of the stem cell therapy; however, it is desired to obtain some gauge of potential efficacy of this cell therapy. Thus, participants will be randomized 1:1 to immediate cellular therapy/deferred sham or immediate sham/deferred cellular therapy. After their first treatment (cellular or sham), participants will be followed for 6 months, at which time

participants who initially received sham treatment will be given stem cell treatment and vice versa. The small sample size is not ideal, but for practical purposes, it would be difficult to increase the sample size significantly without increasing the enrollment period for the study.

Although the study as designed may not be large enough to determine efficacy, some efficacy signals might be observed with the current study design. Such a signal may warrant further investigation of this treatment for CRVO. When a phase II/III randomized controlled trial is planned, appropriate statistical analysis and sample size calculation will be determined.

It is recognized that the study has limited power to show efficacy; however, we hope to obtain some trends in change in visual function or retinal morphology or perfusion that may suggest efficacy to justify a larger randomized prospective clinical trial. Power calculations are presented in the separate Statistical Analysis Plan (SAP) for the proposed method of analyzing the secondary outcomes.

7.9 Data Quality Assurance

The Data Coordinating Center (DCC) will develop and apply data management procedures during the course of this study to ensure accuracy and reliability of data. In addition, the DCC will conduct a site visit prior to study initiation, at study close-out, and approximately biannually during the course of the study as outlined in the Manual of Procedures. In addition, the DCC will be in regular communication, at least monthly, with the Study Chair/PI and/or Study Coordinator(s) regarding any study related issues. These communications and site visits are to ensure that the Enrollment Center is adhering to the study protocol, the study personnel are adequately trained, the facility meets the standards for the study, participant enrollment is progressing as scheduled, and the data collected is of good quality. The collected data will be summarized by the DCC and presented to the DSMC every 6 months or on a schedule approved by the DSMC for review during the course of the study. An annual report of the study progress and interim findings will be submitted to the local regulatory agency and FDA.

8.0 ASSESSMENT OF SAFETY

The safety of intravitreal injection of autologous CD34+ cells isolated from bone marrow will be assessed through regular eye examinations during the 12 months participants are enrolled in the study. Adverse events (e.g., signs, symptoms, disease, syndrome, illness) including new or worsening ocular conditions that occur from the time the participant signs informed consent until the final study visit will be recorded, regardless of suspected cause in accordance with the study protocol and Manual of Procedures. An adverse event (AE) and/or serious adverse event (SAE) form will be completed and the information will be entered into Advantage eClinical.

8.1 Definitions

An adverse event (AE) is any untoward medical occurrence, whether or not considered treatment- or procedure-related, which occurs during the conduct of the study. Medical conditions or diseases present before a participant has study treatment on Day 0 are only considered adverse events if they worsen after the participant has signed ICF (temporal association).

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study treatment caused the adverse event. A reasonable possibility implies that there is evidence that the study treatment caused the event.

An adverse reaction is any adverse event caused by the study treatment.

A Serious Adverse Event (SAE) is defined as any adverse event that suggests a significant hazard, contraindication, side effect, or precaution. This includes, but may not be limited to any of the following events:

1. Death
2. Life-threatening (Life-threatening means that the study participant was, in the opinion of the investigator, at immediate risk of death from the reaction as it occurred.)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4. Inpatient hospitalization or prolongation of existing hospitalization
5. Congenital abnormality or birth defect
6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event
7. Vision-threatening (Refer to Section 8.3, Vision threatening Adverse Events)

Hospitalization or surgery for diagnostic or elective procedures for a preexisting condition is not considered an SAE. A pre-existing condition can be an SAE if the frequency, intensity or character of the condition worsens after signing of informed consent. If any questions arise regarding what may qualify as an adverse event or SAE, the Medical Monitor at the DCC will be consulted.

Unexpected Event or Reaction: An event or reaction is considered “unexpected” when its nature (specificity) or severity is not consistent with applicable product information, such as safety information provided in the package insert, the investigational plan, or the investigator’s brochure.

8.2 Pregnancy

Pregnancy in and of itself, is not regarded as an AE. A confirmed pregnancy in a participant (by urine or blood test) should be reported to the DCC via the Advantage eClinical system as soon as the Investigator has been made aware of the pregnancy. The decision to terminate the participant from the study will be made by the PI or designee and the participant following consultation with the DSMC. The PI or designee will use his/her expert judgment, based on an assessment of the potential benefit/risk to the participant, to determine if it is in the participant's best interest to continue participation in the study.

The pregnancy should be followed until an outcome is known. The outcome of all such pregnancies (i.e., spontaneous miscarriage, elective termination, still births, normal birth or congenital abnormality) must be documented and followed-up on a case report form that will be provided by the DCC. The pregnancy will be followed until an outcome, including any premature termination, must be reported to the DCC. All live births must be followed for a minimum of 30 days or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study. Elective abortion procedures, without complications, should not be considered as AEs unless they require hospitalization.

8.3 Vision Threatening Adverse Events

An adverse event will be considered vision-threatening and reported as an SAE if it has one of the following features:

- A vision loss of > 30 letters on the ETDRS chart compared to the last measurement provided the vision loss lasts > 1 hour.
- Resulting BCVA is light perception or worse for > 1 hour.
- Surgical intervention (including ocular procedures such as laser or cryopexy, intraocular injections, or aspiration of fluid) is required to prevent permanent loss of vision.
- There is severe intraocular inflammation (4+ cell in the anterior chamber or vitreous).
- Medical intervention is required to prevent permanent vision loss in the opinion of the investigator.

8.4 Causality

The Investigator will use the following question when assessing causality of any adverse event to study treatment: Is there a reasonable possibility that the administered cellular product caused the event? An affirmative answer designates the event as a suspected adverse reaction.

In addition, each adverse event will be assessed for its relationship to study procedures, including the injection itself. The Investigator will use the following question when assessing causality of an adverse event to study procedure: Is there a reasonable possibility that the intravitreal injection procedure caused the event?

The Medical Monitor at the DCC is available for consultation on assessing causality. For SAEs, the Medical Monitor will evaluate all reported SAEs against all accumulating knowledge regarding the study treatment. If the Medical Monitor's causality determination differs from the Investigator's assessment, the Medical Monitor's determination will prevail for regulatory reporting purposes.

8.5 Naming and Grading of Adverse Events

Each adverse event will be graded for severity based on the severity grading outlined below:

Grade 1 (Mild) An AE that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Grade 2 (Moderate) An AE that is sufficiently discomforting to interfere with normal everyday activities.

Grade 3 (Severe) An AE that prevents normal, everyday activities. In adults, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.

All adverse events will be followed by the Investigator until resolution or up to one month after study termination or until the study participant is lost to follow-up. The Investigator will treat or observe participants with adverse events as appropriate for standard of care and follow the participants at regular intervals until resolution or stabilization of the adverse event.

8.6 Adverse Event Reporting

Each adverse event will be recorded in the participant's medical record and the adverse event source document will be completed by the Study Coordinator and Investigator. The Study Coordinator completing the adverse event documentation form will be the study coordinator assigned to the visit and may be masked or unmasked depending on the visit. The information will be transmitted to the DCC using Advantage eClinical. All serious adverse events will be reported to the DCC within 24 hours of its occurrence and/or the site's knowledge of the event. All other adverse events will be reported to the DCC within 7 days of the site becoming aware of the event.

8.7 Regulatory Reporting

Death or life-threatening serious adverse events that are related to therapy and unexpected will be reported to the FDA and local regulatory agencies within 7 days. All other adverse events that are serious, related to therapy, and unexpected will be reported to the FDA in 15 days. The initial notification may be via a telephone call or a fax. A written IND Safety Report will be written and submitted within 15 days following the notification of the event.

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APPENDIX A: Ethnic Distribution of Patients Seen at the University of California Davis Eye Center Eye Clinic between 11/1/12 to 10/31/13 Based on Patients' Response

Afghan	0.0%
American Indian/Alaskan	0.0%
Black	1.4%
Cambodian	0.0%
Caucasian	7.3%
Chinese	0.1%
Declined to state	2.2%
Filipino	0.0%
Hispanic or Latino	8.4%
Indo-Chinese Non-Spec	0.0%
Iranian	0.0%
Japanese	0.0%
Korean	0.1%
Laotian/Hmong	0.0%
Mexican American	1.0%
N. African Non-Spec	0.0%
No Response	16.5%
Not Hispanic or Latino	58.6%
Other	2.7%
Other Asian/Mideastern	0.5%
Other Hispanic	0.0%
Other Pacific Island	0.0%
Pakistani	0.0%
Unknown	0.9%
Vietnamese	0.1%
Total:	**100.0%**

APPENDIX B: Determining Childbearing Potential

A female participant who is considered non-childbearing due to a medical condition (i.e., participant has previously undergone a hysterectomy) does not need a pregnancy test, Follicle-stimulating Hormone (FSH) test, or contraception.

If a female participant is considered non-childbearing due to menopause, it must be in accordance with the following guidance on the definition of menopause. This guidance defines menopause as:

Women over age 55 who have not had a period for one year will be considered menopausal and do not need a pregnancy test, FSH test, or contraception.

Women between 50 and 55 who have not had a period for one year should have an FSH test. If their FSH level is ≥ 20 mIU/mL, they will be considered menopausal and do not need pregnancy testing or contraception. If their FSH level is < 20 mIU/mL, they will need pregnancy testing and contraception as required by the protocol.

Women between 45 and 50 who have not had a period for one year will need both an FSH test and a pregnancy test. If they are not pregnant and their FSH level is ≥ 20 mIU/mL, they will be considered menopausal and will not require contraception or additional pregnancy testing. If their FSH test is < 20 mIU/mL, they will need pregnancy testing and contraception as required by the protocol.