PROTOCOL

STUDY TITLE	A Randomized, Active-Controlled, Phase II Study of the Efficacy and Tolerability of Intravitreal Injections of Ranibizumab Compared to Intravitreal Injections of Ranibizumab Combined with Targeted Retinal Photocoagulation in Subjects with Radiation Retinopathy (RRR Study).
STUDY DRUG	Ranibizumab (Lucentis®)
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AMENDMENT	3
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APPENDICES

1. BACKGROUND

1.1. PATHOPHYSIOLOGY

Radiation retinopathy is a common and devastating visual side effect of brachytherapy treatment for uveal melanoma. Treatment methods for visual stabilization or improvement in these patients are sorely needed. Although local tumor control rates in the Collaborative Ocular Melanoma Study (COMS) and other reports are excellent for small to medium-sized choroidal melanoma,[1] long-term visual acuity outcomes have been poor for many patients. In the COMS report examining visual outcomes at three years, 43% of patients have had a visual acuity of 20/200 or worse and 49% had a loss of six or more lines from the pre-treatment level at three years post-treatment.[2] Furthermore, in the COMS, as soon as poor visual outcome was observed, improvement in vision to a level that no longer met the definition of poor vision was rare. The most common reason for irreversible vision loss is radiation retinopathy. In Kaplan-Meier analysis, rates of nonproliferative and proliferative disease at five years after plaque therapy are: 42% and 8%, respectively.[3] Since most epidemiologic studies suggest that there are 1500-2000 new uveal melanomas diagnosed in the U.S. each year, the data suggests that there are likely up to 10,000 patients alive and living with active radiation retinopathy who have been treated with brachytherapy during the past ten years in the U.S. alone.

1.2. TREATMENT OF RADIATION RETINOPATHY

Currently there are no FDA-approved treatments for radiation retinopathy. Small retrospective studies examining off-label use of various agents have been reported.[4-15] Many of these studies were retrospective and/or had small sample sizes. However, these studies suggest that there are beneficial effects on vision and OCT thickness in most patients who were treated on a routine basis for an extended period in most studies.

1.3. RANIBIZUMAB AND RADIATION RETINOPATHY

Thus far, there has been limited published prospective data regarding the routine use of any intravitreal agents for radiation retinopathy. There have been two prospective studies published on the use of Ranibizumab for radiation retinopathy. Most recently, Finger et al. published a Phase I/II open label, non-randomized prospective clinical trial on the use of high dose (2.0 mg) Ranibizumab for recalcitrant radiation retinopathy.[4] Ten patients were enrolled in the study and seven patients completed the protocol. Eight of the ten patients demonstrated a decreased change of central foveal thickness at every time point in the study, but the improvement on OCT did not correlate with significant improvements in visual acuity. Visual acuity in the study overall was stable or improved in 70% of patients over the study time period, a significant improvement over the natural history of the disease.

1.4. NONCLINICAL EXPERIENCE WITH RANIBIZUMAB

1.4.1. Nonclinical Pharmacokinetics

The pharmacokinetics of Ranibizumab has been investigated in rabbits and cynomolgus monkeys following intravitreal and intravenous administration. In both species, following intravitreal administration, Ranibizumab was cleared from the vitreous humor with a half-life of two to three days. Following single intravitreal administration to cynomolgus monkeys, retinal concentrations of Ranibizumab were approximately one-third of vitreous concentrations and declined in parallel with vitreous concentrations. In humans, the intravitreal half-life of Ranibizumab is estimated to be nine days. Repeated intravitreal injections of Ranibizumab can lead to detectable antibodies in serum in rabbits and cynomolgus monkeys.

1.4.2. Nonclinical Toxicology

A series of nonclinical studies of Ranibizumab administered by intravitreal injection to cynomolgus monkeys have been performed (details regarding study design and results can be found in the Investigator Brochure).

1.4.3. Nonclinical Data Supporting the Anti-Edema Activity of Ranibizumab

In studies 01-410E-1757 and 01-401G-1757, the effect of Ranibizumab on vascular leakage was explored using a modified Miles assay in the guinea pig. Ranibizumab demonstrated a concentration-dependent effect of blunting the vascular permeability induced by VEGF. These results are consistent with the decrease in retinal vascular permeability as observed on optical coherence tomography (OCT) and fluorescein angiography in AMD and diabetic macular edema studies and further support rationale for the use of Ranibizumab in CRVO and BRVO, in which vascular permeability plays a significant role in the pathology.

1.5. CLINICAL EXPERIENCE WITH RANIBIZUMAB

Ranibizumab has been or is being studied in more than 5,000 subjects with neovascular AMD in a number of Phase I, I/II, II, III, and IIIb clinical trials. Ranibizumab is contraindicated in patients with ocular or periocular infections and in those with known hypersensitivity to Ranibizumab or any of the excipients in Ranibizumab. Intravitreal injections, including those with Ranibizumab, have been associated with endophthalmitis and retinal detachment. Proper aseptic injection technique should always be used when administering Ranibizumab. Increases in IOP have been noted within 60 minutes of intravitreal injection with Ranibizumab. Therefore, IOP as well as perfusion of the optic nerve head should be monitored and managed appropriately. Serious adverse events related to the injection procedure have occurred in <0.1% of intravitreal injections include endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic

cataract. Other serous ocular adverse events observed among Ranibizumab-treated subjects and occurring in <2% of subjects included intraocular inflammation and increased IOP. The most common adverse reactions (reported ≥ 6% higher in Ranibizumab-treated subjects than control subjects) were conjunctival hemorrhage, eye pain, vitreous floaters, increased IOP, and intraocular inflammation.

Although there was a low rate (<4%) of arterial thromboembolic events (ATEs) observed in the Ranibizumab clinical trials there is a potential risk of ATEs following intravitreal use of inhibitors of VEGF. The rate of ATEs in three studies (FVF2598g, FVF2587g, and FVF3192g) in the first year was1.9% of subjects in the combined group of subjects treated with 0.3 mg or 0.5 mg Ranibizumab compared with 1.1% of subjects in the control arms of the studies. In the second year of study FVF2598g and FVF2587g, the rate of ATEs was 2.6% of subjects in the combined group of those treated with 0.3 mg or 0.5 mg Ranibizumab compared with 2.9% of subjects in the control arm. The most common non-ocular adverse reactions observed in ≥ 15% of Ranibizumab-treated subjects that occurred more frequently than in control subjects included nasopharyngitis, headache, and upper respiratory tract infection.

The Sailor study (FVF3689g)[20] evaluated the safety of intravitreal Ranibizumab in a large population of subjects with CNV secondary to AMD. Subjects in Cohort 1 (N=2378) were randomized (1:1) to receive Ranibizumab at a dose level of 0.3 mg or 0.5 mg; subjects were masked to these dose levels. Treatment was administered monthly for three initial doses (Day 0, Month 1, and Month 2), with scheduled follow-up visits on Months 3, 6, 9, and 12. Retreatment after the first three injections was performed as needed, on the basis of predefined criteria with injections no more frequently than every 30 days.

Cohort 2 (N=1992)[20] consisted of subjects enrolled after the majority of Cohort 1 subjects had been enrolled, with enrollment continuing until Ranibizumab was approved or denied by the FDA for US marketing, and if approved, until commercially available or 30 September 2006, whichever was earlier. Subjects in Cohort 2 received open-label Ranibizumab at the 0.5 mg dose level, with an initial injection on Day 0 followed by retreatment at the physician's discretion, no more frequently than every 30 days. Subjects were monitored for safety for a total of 12 months; safety information, including both serious and nonserious adverse events, was collected at every clinic visit, with two formal safety visits scheduled at Months 6 and 12.

The study consisted of a 30-day screening period and a 1-year treatment period. Treatment duration was approximately 197 days for both dose groups in Cohort 1 and 144 days for subjects in Cohort 2. The mean follow-up time differed between Cohort 1 and Cohort 2, 337 days versus 254 days, respectively.

Ranibizumab was well tolerated, and the incidence of ocular SAEs and AEs was low and unrelated to dose. The rates of individual key ocular SAEs in Cohort 1 were < 1% and were similar across dose groups. Endophthalmitis or presumed endophthalmitis developed in 0.2% subjects in the 0.3 mg group and 0.4% subjects in the 0.5 mg group. The incidence of ocular inflammation, including iritis, uveitis, vitritis, and irdocylitis was 1.9% in the 0.3 mg group and 1.5% in the 0.5 mg group. Overall cataract rates were 5.4% (0.3 mg) and 6.0% (0.5 mg) and were similar when broken down by nuclear, subcapsular, and cortical subtypes. The rates of individual key ocular SAEs in Cohort 2 were <1%.

The rates of key non-ocular SAEs and AEs, including Antiplatelet Trialists' Collaboration (APTC) ATEs, MI, and vascular death were similar for cohorts 1 and 2 and 0.3 and 0.5 mg dose groups. The incidence of MI and non-ocular hemorrhage was similar across Cohort 1 dose groups. APTC ATEs, including vascular and unknown deaths, nonfatal MI, and nonfatal cardiovascular accidents, were similar across dose groups. During the 12-month study period, 0.7% of subjects in the 0.3 mg group and 1.2% of subjects in the 0.5 mg group suffered a stroke. The number of vascular deaths and deaths due to unknown cause did not differ across dose groups. Rates of key non-ocular SAEs in Cohort 2 were generally lower than those in Cohort 1.

Refer to the Ranibizumab Investigator Brochure or Lucentis® Package Insert for additional details regarding clinical safety experience with Ranibizumab.

2. OBJECTIVES

2.1. PRIMARY OBJECTIVE

- Mean change in ETDRS visual acuity at 48 weeks and 104 weeks from Day 0

2.2. SECONDARY OBJECTIVES

- Total number of intravitreal injections required during a 104 week study period (laser versus non-laser)
- Percentage of patients with persistent macular edema based on SD-OCT at 48 weeks and 104 weeks.

3. STUDY DESIGN

3.1. DESCRIPTION OF STUDY

RRR is a phase II, randomized, multicenter, clinical study to assess the tolerability and efficacy of ranibizumab treatment administered in subjects with radiation retinopathy. Subjects will be randomized into one of 3 arms; ranibizumab treatment administered IVT monthly vs. ranibizumab treatment administered IVT monthly combined with peripheral targeted photocoagulation vs. ranibizumab treatment administered IVT for three months followed by as

needed treatment of ranibizumab combined with peripheral targeted photocoagulation over 48 weeks. From week 52 to week 101, all 3 treatment arms will employ a treat and extend protocol for IVT ranibizumab treatment.

3.2. OVERVIEW OF STUDY DESIGN

There is significant scientific evidence to support the concept that radiation-mediated tissue damage involves both inflammatory cascades, as well as innate immunity of the host. This theory is very similar to the disease processes involved with age-related macular degeneration.[4] Epithelial cells, endothelial cells, and fibroblasts participate in angiogenesis, fibrogenesis, and epithelialization to limit the damage caused by radiation to an inflamed tissue and to initiate tissue repair.[4] The triggers for proliferative responses include free radicals and growth factors such as fibroblast (FGF), epithelial (EGF), vascular endothelial (VEGF), platelet-derived growth factors (PDGF) as well as cytokines like TNF-α and IL-1, with macrophages being a major source. Of these triggers, VEGF is the one most well understood in the eye at the present time, and thus is a logical target to limit radiation-induced damage to healthy tissues.

This trial will compare the results of 3 different combinations of therapy to assess the efficacy of peripheral targeted-retinal photocoagulation (TRP) applied to areas of retinal non-perfusion and poor-perfusion combined with ranibizumab injections for the treatment of macular edema secondary to radiation retinopathy. Specifically, this trial will evaluate the ability to reduce the monthly treatment burden by eliminating areas of peripheral ischemia as detected by wide field fluorescein angiography. This peripheral ischemic retina is likely a major VEGF production site. By selectively eliminating these ischemic areas with angiography-guided laser ablation while preserving more perfused areas of peripheral retinal, pathological levels of VEGF may be significantly reduced, translating into fewer necessary monthly intravitreal injections while preserving useful peripheral visual field. The study will include 3 cohorts followed for a total of 104 weeks.

Subjects will be randomized into one of three treatment cohorts in a 1:2:2 ratio.

Day 1 through Week 48:

- Cohort A (n=8) will receive monthly treatment of 0.5 mg ranibizumab for 48 weeks. Monthly treatment is defined as every 28 days (± 7 days).
- Cohort B (n=16) will receive monthly treatment of 0.5 mg ranibizumab for 48 weeks. 1 week (± 3 days) after the initial dose of ranibizumab is delivered, the subject will have peripheral targeted-retinal photocoagulation (TRP) to areas of peripheral retinal ischemia based on wide field angiography that was performed at the screen visit. After the first session of TRP, subjects will have a repeat wide field angiogram at

week 24 and week 36 and will receive additional TRP as needed (PRN) to areas of peripheral retinal ischemia.

- Cohort C (n=16) will receive a loading dose (3 consecutive monthly doses) of 0.5 mg ranibizumab followed by PRN treatment with 0.5 mg ranibizumab. 1 week (± 3 days) after the initial dose of ranibizumab is delivered, the subject will have peripheral targeted-retinal photocoagulation (TRP) to areas of peripheral retinal ischemia based on wide field angiography that was performed at the screen visit. After the first session of TRP, subjects will have a repeat wide field angiogram at week 24 and week 36 and will receive additional TRP as needed (PRN) to areas of peripheral retinal ischemia.

For subjects in Cohort C, PRN treatment of ranibizumab 0.5 mg, starting at week 12 is defined by the Study Drug Retreatment Criteria and Associated Images in Appendix E.

For subjects in Cohort B or Cohort C, PRN treatment of TRP at week 24 and week 36 is defined in Appendix C under TRP Administration and PRN Retreatment Criteria.

Week 52 through Week 101:

All cohorts will enter a treat and extend protocol for IVT ranibizumab retreatment beginning at week 52. At any visit where a dry macula is achieved in the study eye, the visit interval between IVT ranibizumab treatments will be lengthened by 1 week. A dry macula is defined as the resolution of recurrent or persistent fluid based on SD-OCT, slit lamp examination, and/or indirect ophthalmoscopy.

After a subject has been extended beyond a monthly visit interval between IVT ranibizumab treatments, the visit interval will be reduced by 1 week, if the study eye develops recurrent disease activity. Recurrent disease activity is defined as recurrent or persistent fluid based on SD-OCT, slit lamp examination, and/or indirect ophthalmoscopy.

IVT ranibizumab treatment will be administered in the study eye at every visit, no earlier than 7 days before the target date and no longer than 7 days after the target date. The visit interval between IVT ranibizumab treatments is individualized based on each patient's response to treatment. The visit interval between IVT ranibizumab treatments will not exceed 12 weeks.

3.3. OUTCOME MEASURES

3.3.1. Primary Outcome Measures

The primary outcome measures for safety and tolerability are the following:

- Mean change in ETDRS visual acuity at week 48 and week 104 from Day 0.

3.3.2. Secondary Outcomes

- The mean number of intravitreal injections required per subject per cohort.
- Percentage of subjects with persistent macular edema, based on SD-OCT, at week 48 and week 104 compared to Day 0.
- Percentage of subjects avoiding the development of neovascular glaucoma and/or vitreous hemorrhage.

3.4. SAFETY PLAN

The safety assessments to be conducted for this study are listed in Section 4.5.

The safety and tolerability of intravitreal ranibizumab injections have been investigated in previous Phase I, I/II, III, and IIIb studies in AMD, RVO, and DME trials. Potential safety issues associated with the route of administration or the pharmacology of ranibizumab in the study population include decreased BCVA, intraocular inflammation, intraocular infection, transient and/or sustained elevation of intraocular pressure (IOP), cataract development or progression, retinal or intravitreal hemorrhage, macular edema, retinal break or detachment, and arterial thromboembolic events (ATEs). Safety will be assessed by visual acuity, ophthalmic examinations, fluorescein angiograms, B-Scans, OCT, intraocular pressure, vital signs, and adverse event documentation.

To minimize the risks of intraocular infections, all injections will be performed employing sterile techniques as described in Appendix B. Study drug administration will be held for subjects who experience certain ocular events or infections. In the event any subject develops an adverse event in the study eye that is considered by the evaluating physician to be severe in intensity, serious consideration should be given to withdrawing the subject from the study.

The PI or designated Sub-Investigators will review all adverse events on an ongoing basis to determine causality and relationship to study drug and/or study procedures.

3.5. 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 local ethical and legal requirements.

4. MATERIALS AND METHODS

4.1. SUBJECTS

4.1.1. Subject Selection

40 subjects from 4 sites in the United States will be enrolled. Subjects who have provided informed consent will be screened for eligibility before the initiation of any study procedures. Screening evaluations may be performed at any time within 0 – 14 days preceding Day 0. These subjects must have active radiation retinopathy.

The subjects will be randomized in a 1:2:2 ratio so that:

- 8 subjects will receive monotherapy with monthly treatments of 0.5 mg ranibizumab for 48 weeks. Beginning at week 52, all subjects will enter a treat and extend protocol for IVT ranibizumab retreatment. (Cohort A)
- 16 subjects will receive combined therapy with monthly treatments of 0.5 mg ranibizumab and up to 3 sessions of targeted-retinal photocoagulation for 48 weeks. Beginning at week 52, all subjects will enter a treat and extend protocol for IVT ranibizumab retreatment.(Cohort B)
- 16 subjects will receive combined therapy with a loading dose (3 consecutive monthly doses) of 0.5 mg ranibizumab followed by PRN treatment of 0.5 mg ranibizumab and up to 3 sessions of targeted-retinal photocoagulation for 48 weeks. Beginning at week 52, all subjects will enter a treat and extend protocol for IVT ranibizumab retreatment. (Cohort C)

Any patients entering into the study with central vision of 20/50 or better on screening examination will be randomized 1:1:1 into the 3 treatment groups in order to minimize the chance of an accidentally skewed population of patients with good vision in one treatment group. There is no requirement that the study enroll any specific number of patients with good vision.

*See Appendix A, the study flow chart, for screening assessments.

4.1.2. Inclusion Criteria

Subjects will be eligible to participate if the following criteria are met:

- Ability to provide written informed consent and comply with study assessments for the full duration of the study
- Age $\geq$ 18 years
- Active radiation retinopathy resulting from any form of radiation treatment. Radiation retinopathy is defined as any of the following: retinal hemorrhages, exudates, edema, and/or neovascularization, not attributable to other causes.
- Best Corrected Visual Acuity (BCVA) of 20/25-20/400 in the study eye

4.1.3. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

- Pregnancy (verified by positive pregnancy test) or lactation
- Premenopausal women not using adequate methods of contraception. The following are considered effective means of contraception: surgical sterilization, use of oral contraceptives, barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel, an IUD, or contraceptive hormone implant or patch.
- Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated.
- Participation in any other simultaneous medical investigation or trial
- Previous participation in any studies involving investigational drugs within 30 days before Day 0 (excluding vitamins and minerals).
- History of allergy fluorescein, not amenable to treatment
- Previous intravitreal treatment with any anti-VEGF drug within 60 days of Day 0
- Previous intravitreal or subconjunctival treatment with cortical steroids within 90 days of Day 0
- History of vitrectomy
- History of treatment with more than one form of radiation to the eye (e.g. proton beam therapy and plaque therapy).
- Subjects who have more than 7DD of ischemia in the central macula that would hinder visual acuity improvement
- History of panretinal photocoagulation treatment in the study eye.
- Inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analyzed
- Any concurrent intraocular condition in the study eye that, in the opinion of the investigator, could:
    - Require medical or surgical intervention during the 104 week study period to prevent or treat visual loss that might result from that condition.
    - Contribute to loss of at least 2 Snellen equivalent lines of BCVA over the 104 week study period, if allowed to progress untreated.
- Active intraocular inflammation (grade 2+ or above) in the study eye

- Current vitreous hemorrhage in the study eye
- History of rhegmatogenous retinal detachment or macular hole (stage 3 or 4) in the study eye.
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
- Aphakia or absence of the posterior capsule in the study eye.
- Intraocular surgery (including cataract surgery) in the study eye within 2 months preceding Day 0.
- Uncontrolled glaucoma in the study eye (defined as IOP $\geq$ 30 mmHg despite treatment with anti-glaucoma medication).
- History of glaucoma-filtering surgery in the study eye
- History of corneal transplant in the study eye
- Uncontrolled blood pressure (defined as systolic and/or diastolic > 180/110 mmHg while subject is seated). If the subject's initial reading exceeds these values, a second reading may be taken at least 30 minutes later. If the subject requires antihypertensive medication, the subject can become eligible if medication is taken continuously for at least 14 days prior to Day 0 and blood pressure is less than 180/110 mmHg.
- New diagnosis of atrial fibrillation not managed by subject's primary care physician or cardiologist within 3 months of Day 0.
- History of stroke within the last 3 months of Day 0.
- History of myocardial infarction within 3 months of Day 0.
- History of other disease, metabolic dysfunction, or physical examination finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or renders the subject at high risk for treatment complications.
- Active malignancy other than uveal melanoma
- Presence of metastases

4.2. METHOD OF TREATMENT ASSIGNMENT

Upon eligibility confirmation, subject randomization will occur at Day 0 prior to receiving treatment by randomly selecting an envelope containing cohort assignment. Randomization envelopes will be divided into two categories: one for subjects with vision measuring 20/50 or better, and one for subjects with vision

measuring worse than 20/50. Subjects with vision measuring 20/50 or better will be randomized in a 1:1:1 fashion in order to minimize the chance of an accidentally skewed population of patients with good vision in one treatment group. Subjects with vision measuring worse than 20/50 will be randomized in a 1:2:2 fashion. Subjects will be randomized into 1 of the following 3 cohorts:

- **Cohort A**: Subjects receive monthly treatment of 0.5 mg IVT ranibizumab for 48 weeks. Beginning at week 52, all subjects will enter a treat and extend protocol for IVT ranibizumab retreatment.
- **Cohort B**: Subjects receive monthly treatment of 0.5 mg IVT ranibizumab for 48 weeks. 1 week (± 3 days) after the initial dose of IVT ranibizumab is delivered, the subject will have peripheral targeted-retinal photocoagulation (TRP) to areas of peripheral retinal ischemia based on 120° or greater wide field angiography that was performed at the screen visit. After the first session of TRP, subjects will have a repeat wide field angiogram at Week 24 and Week 36 and will receive additional TRP as needed (PRN) to areas of peripheral retinal ischemia. Beginning at week 52, all subjects will enter a treat and extend protocol for IVT ranibizumab retreatment.
- **Cohort C**: Subjects will receive a loading dose (3 consecutive monthly doses) of 0.5 mg IVT ranibizumab followed by PRN treatment with 0.5 mg IVT ranibizumab. 1 week (± 3 days) after the initial dose of IVT ranibizumab is delivered, the subject will have peripheral targeted-retinal photocoagulation (TRP) to areas of peripheral retinal ischemia based on wide field angiography that was performed at the screen visit. After the first session of TRP, subjects will have a repeat wide field angiogram at Week 24 and Week 36 and will receive additional TRP as needed (PRN) to areas of peripheral retinal ischemia. Beginning at week 52, all subjects will enter a treat and extend protocol for IVT ranibizumab retreatment.

4.3. STUDY TREATMENT

4.3.1. Formulation of Ranibizumab

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile, 3 mL stoppered glass vial. Each single-use vial is designed to deliver 0.05 mL of 10 mg/mL ranibizumab aqueous solution with 10 mM histidine *HCl,* 10%, *(-* trehalose dihydrate, and 0.01% polysorbate *20, pH 5.5,* which results in the delivery of a 0.5 mg dose of ranbizumab. Each vial contains no preservative and is suitable for **single use only.**

Further details and molecule characterization will be included in the Investigator Brochure.

4.3.2. Dosage, Administration, and Storage of Ranibizumab

4.3.2.1. Dosage

Subjects will receive intravitreal injections of 0.5 mg ranibizumab according to their specific cohort treatment schedule.

Ranibizumab retreatment criteria for Cohort C, will be based on:

- On SD-OCT, recurrent or persistent fluid
- Treating physician discretion based on clinical evaluation/finding

4.3.2.2. Administration

*See Appendix B for detailed injection procedures.

4.3.2.3. Storage

Upon receipt, study drug kits should be refrigerated at 2°C - 8°C (36°F - 46°F). DO NOT FREEZE. Do not use beyond the expiration date. Ranibizumab vials should remain refrigerated. Protect vials from direct light. Store in original carton until time of use.

RANIBIZUMAB VIALS ARE FOR SINGLE USE ONLY. Vials used for one subject may not be used for any other subject.

4.3.3. Peripheral Targeted Retinal Photocoagulation (TRP)

Subjects in cohort B and C can receive up to 3 sessions of TRP, based on evidence of peripheral ischemia on wide-field fluorescein angiogram. Areas of peripheral ischemia will be selectively treated, preserving areas of more perfused retina. This will minimize any visual acuity loss secondary to non-selective, pan-retinal photocoagulation.

*See Appendix C for TRP administration procedures and PRN retreatment criteria.

4.4. CONCOMITANT AND EXCLUDED THERAPIES

Subjects may continue to receive all medications and standard treatments administered for their systemic conditions at the discretion of their treating physician.

During the 104 week study period, only the treatments mandated by each cohort will be permitted for the study eye. The fellow eye may receive all medications and standard of care therapies necessary.

4.5. STUDY ASSESSMENTS

4.5.1. Assessments during the Treatment Period

**Refer to Appendix A for a schedule of study assessments.*

4.5.1.1. Safety Procedures

Vital Signs (Performed at every visit)

Vital signs will include measurements of pulse and systolic and diastolic blood pressure while the subject is in a seated position. Vital signs should be taken pre-dose at every visit.

B-Scan (Performed at Screen, Week 48, and Week 104, if applicable)

B-scans will be performed, at the discretion of the investigator, three times during the study to ensure the lesion (if any is present) is unchanged. B-scans should be performed per standard of care by qualified site personnel and evaluated by the PI or Sub-Investigators.

4.5.1.2. Efficacy Procedures

Best Corrected Visual Acuity (Performed at every visit)

Visual function of the study eye and fellow eye will be assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985) at 4 meters at every visit.
**See Appendix H for Visual Acuity Testing Protocol*

Intraocular Pressure (Performed at every visit)

Intraocular pressure (IOP) of both eyes will be measured pre-dose at every visit. IOP of the study eye will be measured 30 minutes (± 15 minutes) post-dose. The method used for IOP measurement for a subject must remain consistent throughout the study.

Slit Lamp Examination (Performed at every visit)

Subject's anterior eye structure and ocular adnexa of both eyes will be examined at every visit using a slit lamp, pre-dose, by the PI or Sub-Investigator.

Indirect Ophthalmoscopy (Performed at every visit)

Subject's posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at every visit, pre-dose by the PI or Sub-Investigator.

Optical Coherence Tomography (OCT) (Performed at every visit)

Ocular morphology will be evaluated at every visit using the Heidelberg Spectralis SD-OCT. Starting with the screening visit, images will be captured for both eyes. All OCTs will be electronically archived at the site as part of the

source documentation. Optical coherence tomography technicians must provide previous certification by a reading center, within the last 2 years, or provide evidence of proper training to ensure consistency and quality in image acquisition.
*See Appendix D for OCT protocol

Fundus Photography/Fluorescein Angiography

The anatomical state of the retinal vasculature will be evaluated using Fundus Photography (FP) and wide field Fluorescein Angiography (FA). FP and FA will be captured for both eyes. All FPs and FAs will be archived at the site as a part of source documentation. Photographers must provide previous certification by a reading center, within the last 2 years, or provide evidence of proper training to ensure consistency and quality in image acquisition.

FP and FA evaluations will be performed at screening, Week 24, Week 36, Week 48, Week 78, and Week 104 or Early Termination visit.

* See Appendix D for Imaging Protocol

4.5.2. Early Termination Assessments

Subjects who withdraw from the study prior to completion should return for an early termination evaluation 28 days (± 7 days) following the last injection/study visit for monitoring of all adverse events (serious and nonserious). The schedule of assessments for early termination is the same as that for the final visit.

4.6. SUBJECT DISCONTINUATION

Subjects have a right to withdraw from the study at any time.

The subject may be withdrawn from the study for any reasons: if it is in the best interest of the subject, concurrent illness, adverse events, or worsening condition. Retina Consultants of Houston or the Principal Investigator may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

If a subject discontinues from the study, he or she will not be allowed to re-enter the study.

Reasons for subject discontinuation may include, but are not limited to, the following:

- Sensory rhegmatogenous retinal detachment or Stage 3 or 4 macular hole
- Investigator determination that it is not in the best interest of the subject to continue participation

- Pregnancy
- Need for anti-VEGF therapy other than ranibizumab in the study eye, unless as a part of the prospective investigational study design
- SAE
- Any other safety concerns

In the event of an adverse event in the study eye that is considered by the investigator to be severe in intensity, serious consideration should be given to discontinuing the subject from the study.

4.7. STUDY DISCONTINUATION

Retinal Consultants of Houston or Genentech may terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete

4.8. STATISTICAL METHODS

4.8.1. Analysis of the Conduct of the Study

40 subjects from 4 sites in the United States will be enrolled. Eligible subjects who have provided informed consent will be screened for eligibility before the initiation of any study procedures. Screening evaluations may be performed at any time within 0 – 14 days preceding Day 0. These subjects must have radiation retinopathy with activity seen on SD-OCT, FP or FA.

*See Appendix A, the study flow chart, for screening assessments.

4.8.2. Safety Analysis

Any adverse events, laboratory assessments, physical examinations, vital signs, ocular examinations and measurements from all 40 subjects will be utilized to summarize safety data for this study.

4.8.3. Efficacy Analyses

4.8.3.1. Primary Endpoint

- Mean change in ETDRS visual acuity at week 48 and week 104 from Day 0.

4.8.3.2. Secondary Endpoints

- The mean number of intravitreal injections required per subject per cohort.

- Percentage of subjects with persistent macular edema, based on SD-OCT, at week 48 and week 104 compared to Day 0.
- Percentage of subjects avoiding the development of neovascular glaucoma and/or vitreous hemorrhage.

4.8.3.3. Additional Endpoints

- Percentage of subjects with persistent leakage on FA at week 48 and week 104
- Mean change in foveal thickness per SD-OCT from Day 0 to week 48 and week 104
- Percentage of subjects who experience a gain of 1 or 2 lines in ETDRS BCVA, VA of $\geq$ 20/40 and VA of $\leq$ 20/200 at week 48 and week 104
- Percentage of subjects who experience a loss of 15 or more letters in ETDRS BCVA from Day 0 to week 48 and week 104

4.8.4. Missing Data

Analyses of efficacy and safety will be based on available cases, without imputation for missing values.

4.8.5. Interim Analyses

No formal schedule of interim analyses is planned. Reports of adverse events from this study may be reviewed and summarized periodically while the study is ongoing to ensure the safety of subjects.

4.9. DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

5. ASSESSMENT OF SAFETY

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to {study drug}, all events of death, and any study specific issue of concern.

5.1. ADVERSE EVENTS

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with radiation retinopathy that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., endophthalmitis).

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

5.2. METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

5.2.1. Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 28 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

5.2.2. Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (e.g., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to ranibizumab (see following guidance), and actions taken.

5.3. EVALUATIONS

Medical and ophthalmic history will be obtained at screening visit to review body systems.

Ophthalmologic evaluations will include slit lamp examination, dilated binocular indirect high-magnification ophthalmoscopy, measurements of BCVA, intraocular pressure pre- and post-injection, and B-scan. (See Section 4.5 for a detailed description of the study assessments.)

5.4. VITAL SIGNS

Pulse and blood pressure will be measured at protocol-specified study visits (see Section 4.5).

5.5. PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

5.5.1. Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation timepoints should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

5.5.2. Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

5.5.2.1. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

5.5.2.2. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

5.5.2.3. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.5.2.4. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

5.5.2.5. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the {study drug} should be reported as an SAE.

5.5.2.6. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior {study drug} exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

5.5.2.7. Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

5.5.2.8. AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the investigational product.

The ranibizumab Events of Special Interest are:

- Retinal pigment epithelial tear
- Increased intraocular pressure > 30 mmHg not responsive to maximal topical IOP-lowering drugs measured on two separate days
- Traumatic cataract
- Endophthalmitis
- Intraocular inflammation of > 2+ cell (including vitritis and uveitis)
- Retinal detachment
- ATEs, including stroke

5.5.2.9. Evaluation of Causality

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

- **Yes** – There is plausible temporal relationship between the onset of the AE and administration of the ranibizumab and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the ranibizumab; and/or the AE abates or resolves upon discontinuation of the ranibizumab or dose reduction, if applicable, reappears upon re-challenge.
- **No** – Evidence exists that the AE has an etiology other than the ranibizumab (e.g. preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to ranibizumab administration (e.g. cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

5.5.2.10. Evaluation of Severity

The severity of an AE will be graded by the investigator using a 3-point scale (mild, moderate, or severe).

- **Mild** – dose not interfered in a significant manner with subject's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of the personality of the subject.
- **Moderate** – produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom (including prescription drugs) may be needed.
- **Severe** – Produces significant impairment of the functioning or incapacitation and is a definite hazard to the subject's health. Treatment for symptom may be given and/or subject is hospitalized.

5.6. SERIOUS ADVERSE EVENTS

An AE should be classified as an SAE if the following criteria are met:

- It results in **death** (e.g., the AE actually causes or leads to death).
- It is **life-threatening** (e.g., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs **inpatient hospitalization**. Inpatient hospitalization is defined as admission to a hospital or emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- It results in persistent or significant **disability/incapacity** (e.g., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a **congenital anomaly/birth defect** in a neonate/infant born to a mother exposed to the IMP.
- It is considered a **significant medical event** by the investigator based on medical judgment. May not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above.

Criteria for serious sight-threatening ocular AEs include the following:

- AE causes a decrease in BCVA of **> 30 letters** (compared to most recent assessment of BCVA).

- AE causes a decrease in VA to the level of **light perception or worse**.
- AE requires surgical intervention (e.g. vitreous tap or biopsy with IVT injection of anti-infectives, laser, or retinal cryopexy with gas) **to prevent permanent loss of sight**
- AE is associated with severe intraocular inflammation (e.g. **4+ anterior chamber cell/flare or 4+ vitritis**)
- In the opinion of the investigator, AE may require medical intervention to prevent permanent loss of sight.

5.6.1. SAE Reporting

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682
OR
(650) 225-5288

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

SAE reports that are related to the Ranibizumab and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within 24 hours of the Awareness Date.

SAE reports that are unrelated to the Ranibizumab will be transmitted to Genentech within 24 hours of the Awareness Date.

Additional Reporting Requirements to Genentech include the following:

Any reports of pregnancy following the start of administration with the Ranibizumab will be transmitted to Genentech within 24 hours of the Awareness Date.

All non-serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech.

5.6.2. MedWatch 3500A Reporting Guidelines

In addition to completing appropriate subject demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)

- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

5.6.3. Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including subject identifiers (e.g. D.O.B. initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/medwatch/getforms.html

5.6.4. Additional Reporting Requirements for IND Holders

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of ranibizumab. An unexpected adverse event is one that is not already described in the ranibizumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of ranibizumab. An unexpected adverse event is one that is not already described in the ranibizumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

IND Safety Report can also be reported online:
https://www.accessdata.fda.gov/scripts/medwatch/

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

And to the Site IRB:

Sterling Institutional Review Board Regulatory Department
6300 Powers Ferry Road, Suite 600-351, Atlanta, GA 30339
Tel: (888) 636-1062
Fax: (770) 690-9492

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-5288

IND Annual Reports

Copies to Genentech:

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech.

5.6.5 SAFETY REPORTING FAX COVER SHEET

Genentech
A Member of the Roche Group

Genentech Supported Research
AE / SAE FAX No: (650) 225-4682
Alternate Fax No: (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	
Initial Report Date	
Follow-up Report Date	
Subject Initials (Enter a dash if subject has no middle name)	

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

6. INVESTIGATOR REQUIREMENTS

6.1. STUDY COMPLETION

The following data and materials are required by Retina Consultants of Houston before a study can be considered complete or terminated:

- Clinical data and diagnostic testing from screening through the end of the study
- Copies of protocol amendments and IRB approval/notification
- A summary of the study prepared by the Principal Investigator (will accept IRB summary close letter)
- All regulatory documents (e.g. curricula vitae for each Principal Investigator, U.S. FDA Form 1571 and 1572)

6.2. INFORMED CONSENT

The principles of informed consent are described in ICH Guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/IEC. A copy of the IRB/IEC-approved ICF and documentation of approval must be provided by to the sponsor before study medication will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each subject prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

1. Subjects who can write, but cannot read, will have the ICF read to them before signing and dating the ICF.
2. Subjects who can understand, but who can neither write nor read, will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that the informed consent was given.

The original ICF must be retained by the investigator as part of the subject's study record, and a copy of the signed ICF must be given to the subject.

6.3. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB/EC for review and must be approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB/EC requirements.

The Principal Investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB/EC must be updated at least once a year. The Principal Investigator must also keep the IRB/EC informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB/EC of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the investigator. Some IRBs or ECs may have other specific adverse event requirements that investigators are expected to adhere to. Investigators must immediately forward to their IRB/EC any written safety report or update provided by Retina Consultants of Houston (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.4. STUDY DRUG ACCOUNTABILITY

The Investigator is responsible for the control and distribution of study drug.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure.

6.5. DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, the drug manufacturer and the IRB/EC for each study site, if appropriate.

6.6. RETENTION OF RECORDS

U.S. FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including source documents, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

6.7. STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of

the study should be sent to Genentech. Copies of such reports should be faxed to the assigned Clinical Operations contact for the study:

Lucentis IST Program Fax: 1-866-551-189

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APPENDIX A
Study Flow Chart – Screen through Week 48

	Screen [1]	Day 0[1]	Week 1 (±3 days)	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days)	Week 16 (±7 days)	Week 20 (±7 days)	Week 24 (±7 days)	Week 28 (±7 days)	Week 32 (±7 days)	Week 36 (±7 days)	Week 40 (±7 days)	Week 44 (±7 days)	Week 48 (±7 days)
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed Consent	X														
Demographic Information	X	X													
Medical/ Ophthalmic History	X	X													
Inclusion/Exclusion	X	X													
Randomization		X													
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Scan	X[8]														X[8]
FA/FP	X								X			X			X
Indirect Ophthalmoscopy/ Slit Lamp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TRP Laser[6]			X[6]						X[7]			X[7]			
Study Drug Injection[3]		X[4,5]		X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]

1) Visits 1 and 2 can be combined

2) AEs will be collected from the time informed consent is signed to early termination or end of study

3) Measure IOP pre-dose and 30 (± 15) minutes post-injection

4) Cohort A & B

5) Cohort C, loading dose of 3 ranibizumab injections followed by PRN injections starting at Week 12 if subject meets retreatment criteria (see Appendix E)

6) Cohort B and C

7) Cohort B and C – Additional TRP if subject meets retreatment criteria (see Appendix C)

8) Performed per standard of care at Investigator Discretion

9) Treatment interval between injections based on a treat and extend protocol

10) Mandatory visit, regardless of treatment interval

APPENDIX A

Study Flow Chart – Week 52 through Week 104

	Week 52 – Week 74 (±7 days)	Week 78 (±7 days) [10]	Week 82 – Week 100 (±7 days)	Week 104 (±7 days) [10]
Vital Signs	X	X	X	X
Concomitant Medications	X	X	X	X
Adverse Events[2]	X	X	X	X
BCVA (ETDRS)	X	X	X	X
Intraocular pressure[3]	X	X	X	X
SD-OCT	X	X	X	X
B-Scan				X[8]
FA/FP		X		X
Indirect Ophthalmoscopy/ Slit Lamp	X	X		X
Study Drug Injection[3]	X[9]	X[9]	X[9]	

1) Visits 1 and 2 can be combined

2) AEs will be collected from the time informed consent is signed to early termination or end of study

3) Measure IOP pre-dose and 30 (± 15) minutes post-injection

4) Cohort A & B

5) Cohort C, loading dose of 3 ranibizumab injections followed by PRN injections starting at Week 12 if subject meets retreatment criteria (see Appendix E)

6) Cohort B and C

7) Cohort B and C – Additional TRP if subject meets retreatment criteria (see Appendix C)

8) Performed per standard of care at Investigator Discretion

9) Treatment interval between injections based on a treat and extend protocol

10) Mandatory visit, regardless of treatment interval

APPENDIX B

Injection Procedures for All Subjects

The following procedures will be implemented to minimize the risk of potential adverse events associated with intravitreal injections (e.g., endophthalmitis). Staff will observe aseptic technique involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration. In addition to the procedures outlined below, added safety measures in adherence to specific institutional policies associated with intravitreal injections will be observed.

The technician assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4x4 sterile pads, pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, 0.5% proparacaine hydrochloride, 5% povidone iodine ophthalmic solution, and injection supplies

Pre-Administration

- Instill topical anesthetic (per PI or Sub-I's discretion)
- Method of additional anesthesia will be given at the discretion of each investigator (e.g. subjunctival 2% lidocaine, pledget 4% lidocaine)
- Disinfect the periocular skin and eyelid of the study eye. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Make certain that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects. At investigator's discretion, antiseptic may be used or different antiseptic may be used may be used for periocular preparation.
- The Investigator will glove and place a speculum underneath the eyelids of the study eye.
- Instill 5% povidone iodine ophthalmic solution in the study eye, making sure the drops cover the planned injection site on the conjunctiva.
- Wait a minimum of 30 seconds before intravitreal injection.
- Instruct subject to directly gaze away from syringe prior to injection.

Administration of Intravitreal Injection

- Using aseptic technique, all of the ranibizumab vial contents are withdrawn through a 5µm, 19g filter needle attached to a 1cc tuberculin syringe.
- The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection.
- Replace the filter needle with a sterile needle (size of needle used for intravitreal injection will be at investigator discretion) for the injection.
- Expel the contents of the syringe until the plunger tip is aligned with the line that marks 0.05mL.
- Administer intravitreal injection through the pars plana either inferiorly or superiorly from a temporal approach, 3.5-4 mm posterior to the corneal scleral limbus.

Post-Administration

- Instill 5% povidone iodine ophthalmic solution in the study eye, making sure the drops cover the injection site on the conjunctiva.

- Thoroughly rinse the treated eye with sterile ophthalmic solution.
- Following intravitreal injection, subject's gross visual function will be examined using the follow scale: count fingers, hand motion, light perception, no light perception.
- Measure intraocular pressure (IOP) 30 minutes (±15 minutes) after the injection. Subject will continue to be monitored until IOP is ≤30 mmHg.
- Subjects should be instructed to report any symptoms suggestive of endophthalmitis without delay

If a sites injection procedure differs from what is described above, they can submit their SOP or manual of procedures to Principal Investigator for approval.

APPENDIX C
Targeted-Retinal Photocoagulation (TRP)

Targeted Retinal Photocoagulation can be performed with topical anesthesia, subconjunctival anesthesia or retrobulbar anesthesia as detailed below:

Topical Anesthesia

- Apply topical anesthetic onto the study eye
- Wait 3-5 minutes and apply additional topical anesthetic onto the study eye
- Allow 3-5 minutes for anesthesia to be fully effective before administering laser

Subconjunctival Anesthesia

- Apply topical anesthetic onto the study eye
- In a disposable, sterile, 1cc syringe, draw up 0.5cc of 2% injectable lidocaine without epinephrine with a 27g, ½ " needle
- Replace the 27g needle with a 30g, ½" needle
- The treating physician should administer the lidocaine subconjunctivally in the study eye
- Allow 3-5 minutes for anesthesia to be fully effective before administering laser

Retrobulbar Anesthesia

- Place the subject in a supine position
- Prepare the study eye for local anesthesia by cleaning the injection area directly below the lower lid of the study eye with an alcohol prep pad
- In a disposable, 5cc syringe sterile, draw up 5cc of 2% injectable lidocaine without epinephrine using a 22g, 1 ½" needle
- Replace the 22g needle with a 25g, 1 ½ needle
- The treating physician should insert the needle into the retrobulbar space and inject the lidocaine. After withdrawing the needle, apply firm pressure to the injection site and the eye for about 2 minutes.

TRP Administration and PRN Retreatment Criteria

Laser will be administered to the targeted area of retinal ischemia in the study eye at the treating Investigator's discretion. This laser will be applied with either or both indirect or slit lamp modalities:

- At the initial laser treatment, no less than 200 and no more than 2400 applications will be applied to cover all areas of retinal ischemia, laser power and spot size is at discretion of treating investigator

  At PRN TRP retreatment sessions at Week 24 and Week 36, laser and extent of laser will be applied at treating Investigator's discretion to any newly identified areas of ischemia (non-macular ischemia)

found on wide field fluorescein angiography that were not present at previous TRP session.

1) Patch the study eye for 4-6 hours, if retrobulbar anesthesia is performed, to allow the anesthesia to wear off
2) At the treating Investigator's discretion, subject can be instructed to use prednisolone acetate ophthalmic solution to reduce inflammation

Appendix D
Imaging Protocols

Masked subject data should be entered as follows:

Last Name: RRR
First Name: Subject Initials and Study ID number
DOB: actual date of birth of subject
Sex should be answered

SD-OCT

SD-OCT will be performed at study sites on a Spectralis OCT instrument (Heidelberg). At each study visit SD-OCT images of both eyes should be captured. Foveal thickness and mean central subfield thickness should be recorded at every study visit. OCT scans should be performed as follows:

- Brown-Keg Scan (build)
  - 20° x 20°
  - 49 cuts
  - 9 ART

Scans should be centered on the fovea. After initial scan set as a reference and all subsequent OCT's done to reference.

Color Fundus Photo Photography

Fundus Photos of both eyes should be taken in stereo pairs of:

1) Fundus Reflex
2) 30° Field of F1, F2, F3

Instrument used to capture fundus photos is at the discretion of the investigator.

Wide Field Angiography

The instrument used to capture the angiography is at the discretion of the investigator..

The posterior pole should be centered throughout the entire angiogram.

Fluorescein angiography is performed in the usual manner (intravenous injection of 2.5 ml of 5% or 5 ml fluorescein solution). Inject fluorescein as rapidly as possible using a 21 or 23 gauge infusion set. The study eye will be the transit eye.

- Take a picture of the study eye as soon as the fluorescein dye has been completely injected
- Pictures should be taken of the study eye at first sign of dye through complete venous filling as well as at 1 minute, 2 minutes, 5 minutes and 6 minutes after fluorescein dye has been injected
- Pictures of the fellow eye should be taken 2 and 5 minutes after fluorescein dye has been injected.

At completion of documenting dye transit take a high magnification image of the study eye (if using a Heidelberg ensure to use high resolution setting)

B-Scan

B-scan should be performed per standard of care at Screen, Week 48 and Week 104, at investigator discretion, by qualified site personnel and evaluated by the PI or Sub-Investigators.

Appendix E
Study Drug Retreatment Criteria and Associated Images

Clinical evidence of recurrent active radiation retinopathy necessitating treatment with intravitreal injection of ranibizumab 0.5 mg includes any of the following:

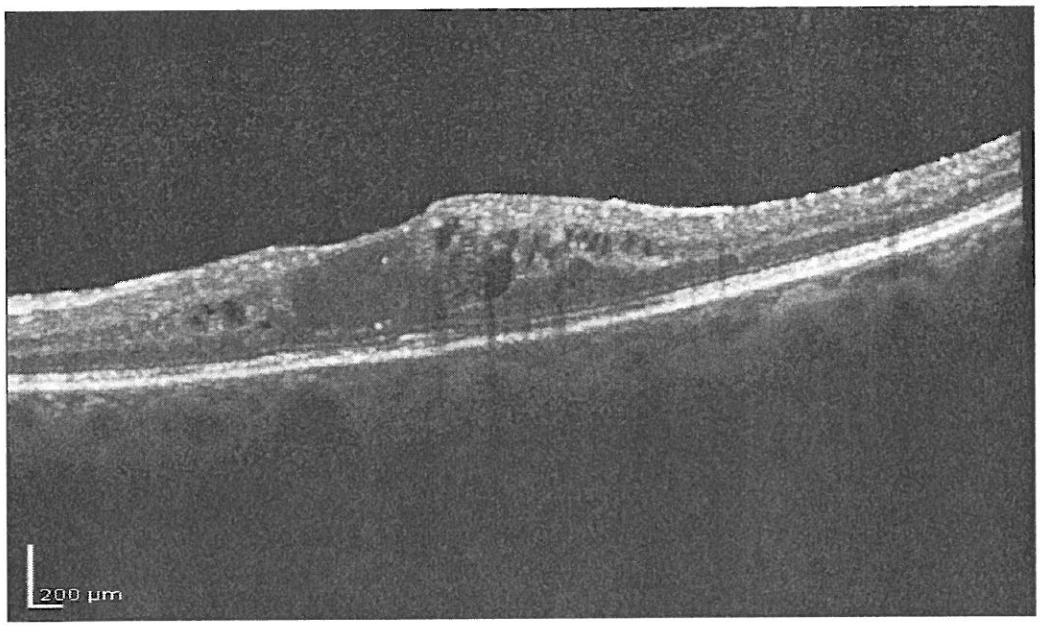
1. Evidence of true subretinal or intraretinal fluid in the study eye on SD-OCT.
2. Increase in central subfield thickness on SD-OCT of 50 microns or more due to active radiation retinopathy.
3. ETDRS vision loss of 5 letters or more from the previous measurement with corresponding SD-OCT evidence of active disease activity in the macula.

A "dry" macula with no clinical evidence of active radiation retinopathy that does not necessitate treatment with intravitreal injection of ranibizumab 0.5 mg is defined by the following:

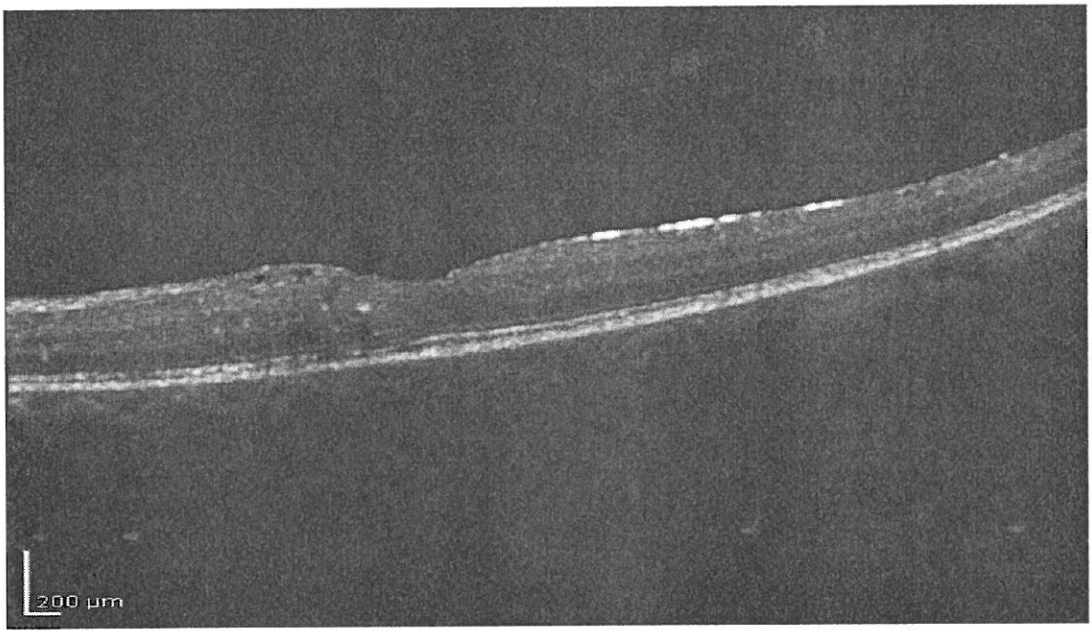
1. Resolution of active radiation retinopathy on both clinical and SD-OCT evaluation with resolution of intraretinal or subretinal fluild in the study eye.
2. Hypo-dense areas not consistent with true subretinal or intraretinal fluid or active disease activity do not necessitate treatment.
3. Small chronic intraretinal cystic areas observed on SD-OCT associated with outer-retinal atrophy believed to not be affecting visual acuity in the study eye do not necessitate treatment. These cysts, when present while considering the macula dry, should be marked in the SD-OCT interpretation area on the chart note.
4. Minimal increased retinal thickening in the study eye on SD-OCT without definitive intraretinal or subretinal exudative fluid does not necessitate treatment.

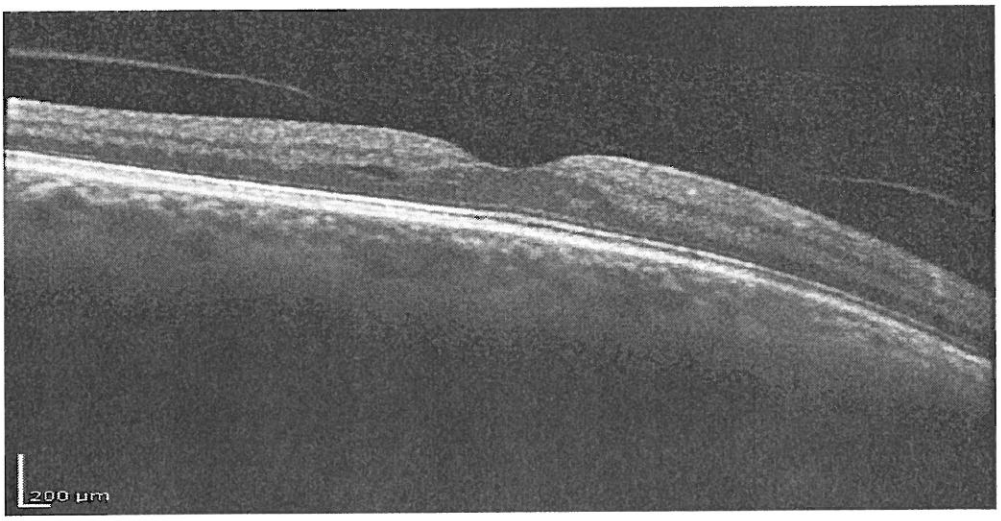
Associated Images

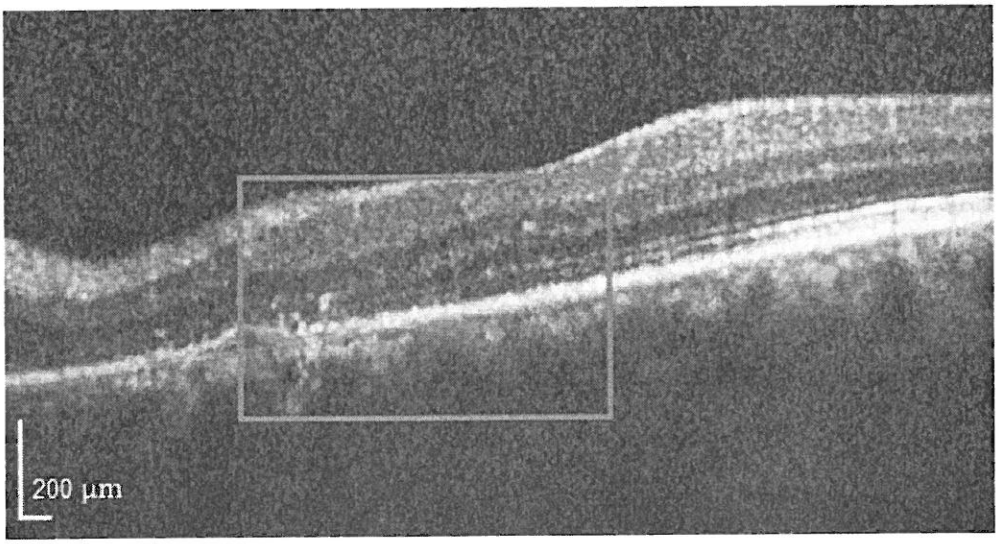
SD-OCT Findings Consistent with Active Radiation Retinopathy or Exudative Disease Activity **Necessitating Treatment** with Intravitreal Injection

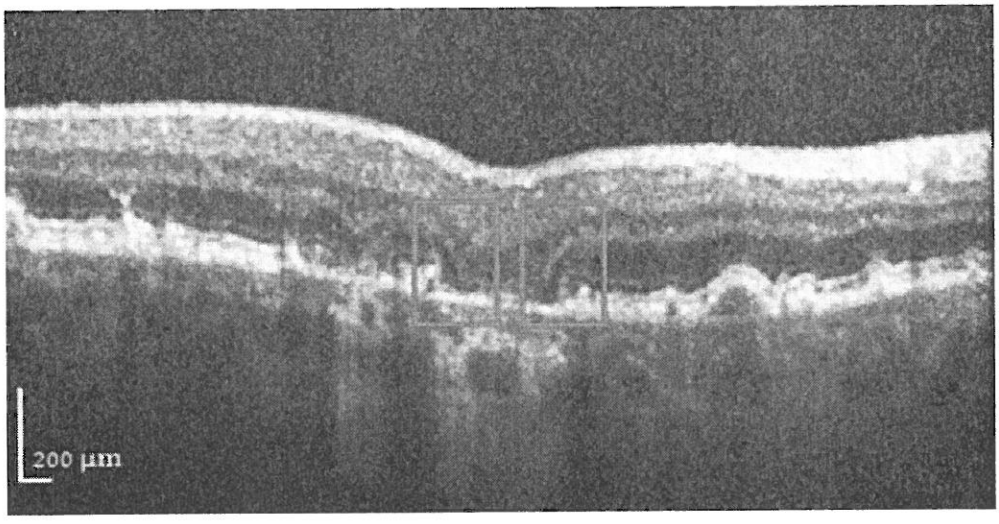


SD-OCT Findings Consistent with Inactive Radiation Retinopathy **Not Requiring Treatment** with Intravitreal Injection




200 µm


200 µm


200 µm

ppendix F
Grading Scale for Intraretinal Hemorrhages, Hard Exudates, and Neovascularization

The severity of intraretinal hemorrhages, hard exudates, and neovascularization in the study eye should be assessed through slit lamp and/or indirect examination by the PI or Sub-Investigator. The PI or Sub-Investigator should grade the severity of intraretinal hemorrhages, hard exudates, and neovascularization based on the grading scale below.

Intraretinal Hemorrhages

The grading scale below is measured by individual hemorrhage. This grading scale should be used to measure the severity of intraretinal hemorrhages in the study eye.

Grading Scale	Interpretation
0	None
1	0 - 5
2	5 - 10
3	10 - 20
4	➢ 20

ard Exudates

The grading scale below should be used to measure the severity of hard exudates in the study eye.

Grading Scale	Interpretation
0	None
1	Presence of non-visually significant hard exudate(s)
2	Presence of macular visually significant hard exudate(s)

Neovascularization

The grading scale below should be used to measure the severity of neovascularization in the study eye.

Grading Scale	Interpretation

0	None
1	Early neovascularization including IRMA or non-clinically apparent neovascularization detectable on FA but minimally detectable on exam
2	Clinically apparent neovascularization including NVI, NVD, and/or NVE
3	Neovascular glaucoma with documented elevated IOP requiring IOP therapy

Appendix G
Analysis of Similar Events Template for IND Safety Reports

IND Safety Report

Case Summary

This section will be initiated by a research coordinator and may be modified by principal investigators if necessary. The case summary should describe the reported AE in detail, including a description of what happened and a summary of all relevant clinical information (e.g. medical status prior to the event, signs, symptoms, diagnoses, clinical course, treatment, outcome, etc.) The IND safety report should not identify the subject ID #, reporting investigator, or the site as this information may compromise the study blind.

PREVIOUS REPORTS

The information for this section comes from Principal Investigator and the search of similar events. This section should be written by the responsible principal investigator.

* *Select one of the following two statements after reviewing the search of similar events results.*

Under IND _____(insert IND#), the following IND safety reports of similar AEs have been previously submitted:

IND	Reported Event	Submission Date

Or

Under IND _____ (insert IND#), no IND safety reports of similar AEs have been submitted previously.

In addition to previously submitted IND safety reports of similar events, this section can also summarize pervious serious reports of the same/similar event that were considered unrelated to the investigational product at the time of the reporting. These events would remain blinded, unless a decision to unblind is made by an Independent Monitoring Committee for reasons of subject protection. The decision on what similar events to summarize in this section should be made after reviewing the similar events report generated by Clinical Data Management. If a safety signal is particularly worrisome (e.g., a study stopping type of event), a more extensive evaluation may be required.

Assessment of Relationship

After evaluation the new case report and reviewing any relevant previous reports of similar events, e PI selects one of the following boilerplate conclusion statements, if applicable. The PI may also craft an alternative conclusion.

Based on review of available data, **Retina Consultants of Houston** believes there is a reasonable possibility of a cause-and-effect relationship between administration of _____(insert study drug name) and the occurrence of _____(insert AE).

Additional information on risk factors and/or treatment of the AE may be provided if warranted.

Or

Based on review of available data, the **Retina Consultants of Houston** does not believe that there is a reasonable possibility of a cause-and-effect relationship between administration of _____(insert study drug name) and the occurrence of _____(insert AE).

Explain if warranted. Do not speculate.

Or

Based on review of available data, the **Retina Consultants of Houston** cannot establish or exclude the possibility of a cause-and-effect relationship between administration of _____(insert study drug name) and the occurrence of _____(insert AE).

Explain if warranted. Do not speculate.

After review of the clinical details and investigator's comments pertaining to this AE, and based on experience to date, the **Retina Consultants of Houston** does not believe that changes to the nduct of this clinical trial are warranted. *This statement can be modified if changes to the conduct of the clinical trial are made*

Appendix H
EST CORRECTED VISUAL ACUITY PROTOCOL

1. Visual Acuity Equipment and Facilities

1.1 Introduction

The visual acuity of participants will be measured consistent with the standard procedure developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) and adapted for the Age Related Eye Disease Study (AREDS). The procedure is described in this section. The following equipment is used: a set of three charts (second edition), which are modified ETDRS Charts 1, 2, and R and a retro illuminated box providing standardized chart illumination, as modified from the design by Ferris and Sperduto.

The charts and boxes could be provided by:

Optelec featuring Lighthouse Products
3030 Enterprise Court, Suite C
Vista, CA 92081
Telephone: 800-826-4200
Fax: 800-368-4111

Precision Vision
944 First Street
La Salle, IL 61301, USA
Telephone: 800-772-9211
Fax: 815-223-2224

Sussex Vision Intl. Ltd.
A2, Dominion Way
Rustington
West Sussex BN16 3HQ, United Kingdom
Telephone: 01903 851951
Fax: 01903 767732
www.sussexvision.co.uk

Visual acuity testing is required at a distance of 4 meters and, for participants with sufficiently reduced vision, at 1 meter. The 4 meter distance should be marked clearly and permanently; the 1 meter distance must be measured with a 1 meter stick with the participant in a chair (Section 1.5).

1.2 Visual acuity charts

Charts 1 and 2 are used for testing the right and left eye, respectively, and Chart R is used for refraction. The features of the charts are high-contrast Sloan letters of equal difficulty, 5 letters in each of 14 lines, and a geometric progression of letter size (and, thus, an arithmetic progression of the logarithm of minimum angle of resolution [LogMAR]) from line to line. Charts 1, 2, and R have different letter sequences. Participants should be prevented from seeing Charts 1 and 2 until refraction has been completed and the visual acuity test begins.

1.3 Visual acuity box

The dimensions of the light box are 24 and ¾ inches (62.9 cm) by 25 and ¾ inches (65.4 cm) by 7 inches (17.8 cm). The box can be mounted on a wall, on a countertop, or on a cylindrical stand manufactured by Optelec featuring Lighthouse Low Vision Products or Precision Vision. The stand

is mounted on a five-pronged wheelbase, with each prong about 14 inches (35.6 cm) long. Two of the five wheels are lockable. When the box is mounted on the stand, its height can be varied.

The light box should be mounted or placed at a height such that the top of the third row of letters (0.8 LogMAR) is 49 ± 2 inches (124.5 ± 5.1 cm) from the floor.

The rear of the box provides storage space for the two charts not being used.

1.4 Illumination

Most of the room lights should be turned off during the visual acuity test. The box itself provides sufficient illumination for the examiner to record the test results. Additional light can have an adverse effect. With the box light off, not more than 15 foot candles (161.5 lux) of light should fall on the center of chart.

To measure the amount of light, the room is set up as for the visual acuity test but with the box lights off. The light meter is placed approximately 48 inches (1.22 meters) from the floor with its back against the chart. The amount of light is measured and the room is darkened, if necessary.

The visual acuity light box is equipped with two Daylight 20-watt fluorescent tubes. Because the illumination of fluorescent tubes diminishes by 5 percent during the first 100 hours and by another 5 percent during the next 2,000 hours:

- New tubes should be kept on for 96 hours, which does not have to be continuous; and
- All tubes should be replaced once a year (every 12 months). Clinical centers must maintain a written log with the date (month, day, and year) of the last change of tubes. It is recommended that this log be kept on the back of the light box. Status of tubes will be checked periodically.

The fluorescent tubes should also be checked periodically for proper functioning. Replacement tubes can be purchased at a local store or from Lighthouse Low Vision Products or Precision Vision.

Each tube is partially covered by a 14-inch (35.6 cm) fenestrated sleeve, open in the back, which serves as a baffle to reduce illumination. Each sleeve should be centered on the tube such that an equal length of tube, (approximately 4 and 3/16 inches or 10.6 cm) is left uncovered to the right and left of the sleeve. The openings in the backs of the sleeves should be oriented to point directly toward the back of the box (i.e., the sleeves should not be titled up or down). The lower sleeve may have a cutout that should point down toward the ballast, although all boxes manufactured since 1997 lack this feature.

1.5 4 and 1 meter visual acuity lanes

A distance of exactly 4 meters (13 feet and 1.5 inches, or 157.5 inches) is required between the participant's eyes and the visual acuity chart for the 4 meter test, and a distance of exactly 1 meter (39 and 3/8 inches) is required for the 1 meter test.

The room for visual acuity testing must have, in addition to the 4 meter lane, space for the visual acuity box (and possibly a stand) and space for the participant. Minimum room-length requirements vary according to how the box is mounted and whether the participant sits in a chair or stands for the 4 meter test.

1. Wall-mounted box: In addition to the 4 meter lane, 7 inches (17.8 cm) must be allowed for the depth of the box plus space for the participant to sit or stand.

2. Stand-mounted box: In addition to the 4 meter lane, 13 inches (33 cm) must be allowed for two of the stand's casters to touch the rear wall (or a line marked on the floor when there is no wall) plus space for the participant to sit or stand.

1.6 Marking the distance

4 meters

1. If the chair and visual acuity box are permanently affixed, distance measurements need to be made only once and the wall should be clearly marked in order to properly align each individual study subject while being tested.

2. If the box is mounted on the wall but the participant's chair is not permanently affixed, the 4 meter distance of the participant's eye from the chart must be marked clearly and permanently both on the floor and the wall closest to the subject's chair.

3. If the box is mounted on a movable stand, the 4 meter distance must be marked clearly and permanently on the floor and on the wall. The location and orientation of the box must be rechecked each time a new chart is put in place or the box is touched. Two of the five casters should touch the wall or face the rear orientation.

1 meter

The 1 meter distance is measured from the front of the eye of the participant, seated comfortably in a chair – with a non-flexible back and without wheels – with his or her back firmly placed against the chair's back in a straight line to the front of the chart. The meter stick may be homemade (e.g., a dowel rod) or purchased at a local hardware store or by mail.

2. Refraction Technique

2.1 Introduction

The technique described below is required for participants whenever a manifest refraction and best corrected visual acuity measurement is indicated by the study protocol. Any standard visual acuity chart such as Refraction Chart R or a Project-O-Chart, and any test distance can be used for determining the best lens correction in each eye. This is permitted so that any refraction room at the Clinical center can be used, minimizing waiting time for the participant. If the standardized test (4 meters, Chart R) is not used, however, an over-refraction with spheres should be done with Chart R at 4meters prior to testing visual acuity (Section 2.7, Adjustment for non-standardized test conditions). Charts 1 and 2 are not used for refraction, only for visual acuity testing. The right eye is refracted first and then the left eye, both at 4 meters before any testing at 1 meter.

2.2 Beginning approximate refraction

If the participant wears contact lenses and has glasses, he or she should be told not to wear the contact lenses on the day of the examination. If the participant presents for the examination wearing contact lenses (because he or she has forgotten to follow the instructions or because he or she has no glasses), the contact lenses should be removed and refraction and visual acuity testing should not begin for at least one-half hour.

The result of a subsequent refraction on a previous visit can be used as the beginning approximate refraction. If this is not available, the procedures described below should be followed.

1. If the participant's uncorrected visual acuity is 20/200 (LogMAR 1.0) or better and the participant does not have glasses for distance vision, the beginning approximate refraction is no lens correction (plano).
2. If the participant's uncorrected visual acuity is less than 20/200 (LogMAR 1.0) in either eye with the participant's present distance glasses (or without correction, if the participant does not have glasses), retinoscopy should be performed by an examiner proficient in the procedure. An acceptable alternative is to conduct an arbitrary trial with any lenses to bring acuity to 20/200 (LogMAR 1.0) or better. Another is to use an automated refractor. The lens corrections obtained are used as the beginning approximate refraction for determining best corrected visual acuity (Section 3).
3. If the participant's visual acuity is 20/200 (LogMAR 1.0) or better with the participant's present distance glasses, the glasses are measured with a lensometer, and these measurements are used as the beginning approximate refraction.

If the participant's visual acuity measures worse than 20/200 (less than 4 letters at 4 meters) due to decreased vision or an inability to cooperate, special refraction and visual acuity measurement procedures may be required for participants who have reduced visual acuity or difficulties in cooperating with the examination (see Section 2.7).

2.3 Subjective refraction

The trial frame is placed and adjusted on the participant's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. It is permissible to use a

phoropter for subjective refraction. However, for testing visual acuity (Section 3), the lenses from the final phoropter refraction must be placed in a trial frame, and the final sphere must be rechecked as described in Section 2.6, Refining final spherical power. The left eye is occluded, and the beginning approximate refraction – as determined above – is placed in the right lens cells with the cylindrical correction anterior. If Chart R is used, it should be read at a distance of 4 meters. Other standard eye charts may be read at a distance of 10 to 20 feet directly or with a mirror (if visual acuity is too poor for the participant to see the largest letters on the chart at this distance, Section 3.2, 1 meter test)

2.4 Determination of spherical refraction

Refer to the following chart when selecting testing lens powers:

	Check Sphere First		Check Cylinder Axis then Cylinder Power			Final Sphere Refinement	
If VA on R chart is between:	Power	Give	Axis	Power	Give	Power	Give
20/10 to 20/80 (4 meters)	+0.50 -0.37 +0.50	+0.50 -0.25 +0.50	0.25 JCC	0.25 JCC	+0.25 -0.25	+0.25 -0.37 +0.25	+0.25 -0.25 +0.25
20/100 to 20/160 (4 meters)	+1.00 -1.00 +1.00	+1.00 -1.00 +1.00	0.50 JCC	0.50 JCC	+0.50 -0.50	+0.50 -0.50 +0.50	+0.50 -0.50 +0.50
20/200 to 20/400 (4 or 1 meter)	+2.00 -2.00 +2.00	+2.00 -2.00 +2.00	1.00 JCC	1.00 JCC	+1.00 -1.00	+1.00 -1.00 +1.00	+1.00 -1.00 +1.00
<20/400 (1 meter)	+2.00 -2.00 +2.00	+2.00 -2.00 +2.00	No cylinder test required			No refinement required	

The visual acuity of the right eye is assessed and noted. If beginning visual acuity on Chart R is between 20/10 and 20/80, a +0.50 sphere is then held in front of the right eye and the participant is asked if the vision is "better," "worse," or "no different" while he or she is looking at the smallest line read well. If beginning visual acuity on Chart R is worse than 20/80, refer to the above chart for lens power and increment guidelines.

1. If vision is improved or there is no change, the sphere in the trial frame is replaced with one that is one-half diopter more plus. The +0.50 sphere is again held in front of the right eye, and the participant is asked again if the vision is "better," "worse," or "no different." This process of increasing the plus sphere in the trial frame is repeated until the participant states that the +0.50 sphere held in front of the trial frame makes the vision worse. When the participant responds that the vision is made "worse," the lens

should be left in place for 10 to 15 seconds in an attempt to evaluate whether the participant is accommodating (an unlikely situation in a population over age 60). If the vision clears during this period, the +0.50 may be added again and succeeding attempts to evaluate additional plus lenses should be accompanied with a 10 to 15 second delay. If there is no evidence of unrelaxed accommodation, the delay period while assessing plus lenses is not necessary at any time further in the examination.

2. Whenever the participant says that the vision is "worse" and remains worse, the +0.50 sphere is removed from in front of the trial frame.

By this process, the highest plus or least minus sphere that is tolerated without blurring the participant's vision is determined. After determining this highest plus or least minus sphere, the participant is asked to read the smallest line possible.

Next, a -0.37 sphere is held in front of the trial frame, and the participant is asked if the vision is "better," "worse," or "no different."

1. If vision is improved, the participant is requested to read the chart and if at least one more letter is read, the sphere in the trial frame is replaced by a sphere that is 0.25 diopter less plus.

   In certain situations, the participant is unable to read more letters, but is convinced that the vision is actually improved. If the examiner believes that this is the case, the additional minus lens may be added. At any stage in the examination, no more than 0.25 diopters of minus should be added without an increase in the number of letters read correctly. The additional minus lens should not be added if the participant reads fewer letters but states that acuity is better. There is a general attempt in this refraction protocol to avoid "over-minusing" the participants. However, when plus cylinders are in the refraction, one must be careful not to unnecessarily withhold minus which may be necessary for the participant to accept the needed plus cylinders later in the refraction. Minus spherical power is added in -0.25 diopter increments until the participant shows no further improvement in vision. Once minus lenses no longer improve vision, again offer a +0.50 sphere to determine if more plus would be accepted. Always end up offering plus power.

2. If the participant says the vision is "no different" or "worse," no minus power should be added, and the spherical determination is complete.

2.5 Determination of cylindrical refraction

For purposes of this discussion, only plus cylinder techniques are presented.

1. Cylinder axis determination:
   If the beginning approximate refraction contains a cylinder correction, changes in cylindrical axis are tested by adding a 0.25, 0.50, or 1.00 diopter cross cylinder (refer to chart under Section 2.4), first with the positive axis 45 degrees to one side of the cylinder axis, and then with the positive axis 45 degrees to the opposite side of the cylinder axis.

Since neither position may produce a clear image, the participant is encouraged to select the position producing the least blur while fixing on a single round letter on the line above the lowest line on the chart he or she is able to read when the cross cylinder is not held up before the trial frame.

If the participant cannot choose between the two positions of the cross cylinder at the beginning of this test, the axis of the cylinder is moved 5 to 15 degrees, first in one direction and then in the other, with the cross cylinder being checked in each position to confirm that the original axis was indeed correct.

If the participant prefers one position of the cross cylinder to the other and the cylinder in the trial frame is plus, the axis of the cylinder is moved 5 to 15 degrees toward the positive axis of the cross cylinder when it is in the position found to be less blurry by the participant. As axis refinement progresses, it may be necessary to move the cylinder axis by less than 5 degrees, depending upon the participant's responses to axis test. (When the power of the cylinder is low or the participant's discrimination is poor, larger shifts will produce more clear-cut answers).

The cross cylinder is tried again with the positive axis 45 degrees first to one side and then to the opposite side of the new cylinder axis to determine which position is producing less blur. If the participant find one position less blurry, the axis of the plus cylinder is moved toward the positive axis of the cross cylinder. Testing for change of axis is repeated until the participant finds neither position definitely better than the other.

2. Cylinder Power Determination:
Change in cylinder power is tested by adding the cross cylinder, first with the positive axis and then with the negative axis coincident with the cylinder axis. For this test, the participant is requested to focus attention on a round letter on the lowest line on the chart he or she is able to read.

If the participant prefers the positive axis coincident with the cylinder axis, the power of the correcting plus cylinder is increased by an additional +0.25 diopter. If the participant prefers the negative axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. The process is repeated until the participant finds neither position definitely better than the other.

As plus cylinder is added, the examiner should recognize that the spherical equivalent of the refraction is being changed. More minus spheres may be needed as plus cylinders are added. When using plus cylinders, for every 0.50 diopter of cylinder power added, the sphere should be changed by – 0.25 diopter. If at any time, the preference with the cross cylinder indicates that cylinder power should be removed entirely; the 0.25 cylinder should be rotated 90 degrees from its original position. The axis should be refined and the power should be tested again.

If the beginning refraction is a "pure" sphere, the presence of astigmatism is tested by arbitrarily placing a +0.25 cylinder at 180 degrees in the trial frame, after having

determined the highest plus or least minus sphere producing minimal blurring of vision, as described above. The refraction is then continued by using the cross cylinder to test for cylinder axis and then cylinder power using the technique outlined above. If at any time the preference with the cross cylinder indicates that cylinder power should be removed entirely, the 0.25 cylinder should be rotated 90 degrees from its original position, and the power should be tested again. At this point, if the participant prefers additional power, it should be added. If, on the other hand, the participant prefers to remove the +0.25, it should be removed and the final refraction is then purely spherical. An example of the procedure follows:
Beginning refraction: -2.50 + 0.25 axis 90 degrees. Use of the cross cylinder to check cylinder axis indicates that the participant prefers the 90 degree axis. If, on using the cross cylinder to check cylinder power, the participant wants the 0.25 cylinder removed, rotate the cylinder to 180 degrees and test for cylinder power again. If additional power is preferred, it should be added, remembering to adjust sphere as needed. If the preference with the cylinder at 180 degrees is to remove the 0.25 cylinder, this should be done, and the resulting refraction is -2.50 sphere.

Minus cylinders may be used instead of plus cylinders to determine the best correction for the cylinder power and axis. If minus cylinders are used, the above procedure must be revised to reflect the change in sign.

2.6 Refining final spherical power

When neither the power nor the axis of the cylinder can be improved, the power of the sphere is refined by testing with +0.25 sphere and -0.37 sphere, and changing the spherical power as indicated in Section 2.4. If the sphere is changed at this point, the cylinder should be rechecked. This process is repeated until no further significant lens changes are made.

This refraction protocol can be summarized as follows: First, having eliminated any possible accommodation with plus spheres, the spherical equivalent power is placed on the retina. Then, the cylinder power and cylinder axis are assessed. This process of checking sphere, cylinder axis, and cylinder power is repeated until there are no changes that result in an increased number of letters being read. Ideally, at the end of the refraction, the sphere is checked, and the participant neither tolerates increased plus nor improves with increased minus spheres. Then, the axis is checked, and no change in axis is indicated. Finally, the cylindrical power is checked, and no change in this is indicated. At this point, the refraction is completed. Sometimes this endpoint cannot be reached because there are an unending number of small corrections at each repetition of the process. When it becomes clear that these small changes are not resulting in an increased number of letters read correctly, the examiner can terminate the refraction.

The lens corrections obtained in this way for the right eye are recorded on the Refraction Worksheet as the corrections obtained by subjective refraction for the right eye. The entire process is repeated for the left eye, and these lens corrections are also recorded on the Refraction Worksheet as the corrections obtained by subjective refraction for the left eye.

2.7 Adjustment for non-standardized test conditions

If a test distance other than 4 meters is used for refraction and in a location other than the certified visual acuity lane (Section 1.5), a final refinement of the spherical power (as outlined in Section 2.6, Refining final spherical power) should be performed in the certified lane at 4 meters just before visual acuity testing, using Refraction Chart R with appropriate lighting. If the refinement power differs from the initial refraction, this lens correction should be recorded on the Visual Acuity Worksheet. Similarly, if a phoropter is used for the subjective refraction, a final check of the spherical power (as described in Section 2.6) should be performed with a trial frame using the 4 meter refraction lane and Refraction Chart R. A change of spherical power in these circumstances only requires rechecking the cylinder power if the sphere changes by 0.50 diopters or more.

2.8 Refraction for participant with poor visual acuity

If it is not possible to perform refraction at the 4 meter distance because of decreased vision or impaired mental aptitude, which prohibits the participant from correctly reading 4 or more letters, the refraction should be attempted at 1 meter. Before attempting the 1 meter refraction, +0.75 sphere must be added to the last 4 meter refraction obtained (during follow-up this is the previous refraction result obtained from the refraction data sheet), which is to be used as the starting refracting. If the subjective refraction can be successfully performed at 1 meter, a +0.75 sphere should be subtracted from the final 1 meter refraction to make the correction appropriate for the 4 meter distance. The refraction procedure at 1 meter is the same as the procedure for 4 meters. However, if the participant is unable to discern changes in letter clarity using the lens increments outlined for the 4 meter refraction, larger increments of lens power should be used. When checking the sphere, ± 1.00 diopter should be tested. If the participant still cannot perceive any difference in clarity, changes up to ± 3.00 diopters can be attempted. Cylindrical refraction can be assessed with the 0.50 or 1.00 diopter Jackson cross cylinder rather than the 0.25 diopter cross cylinder. When changing the sphere power, use 1.00 diopter increments for adding plus, and 0.50 diopter increments for adding minus. When changing cylinder power, add or subtract cylinder power in 0.50 diopter increments.

If at the end of the refraction process at 1 meter (still on Chart R), the participant is consistently reading letters on the seventh line or lower, he or she should be moved back to 4 meters, and the procedures for the 4 meter refraction should be followed (still using Chart R).

As always, when testing final visual acuity the testing is started at 4 meters (using Charts 1 and 2).

If it is not possible to perform a subjective refraction at the 4 meter distance because visual acuity is too poor for the participant to see the largest letters on the refraction chart at this distance, the refraction should be attempted at 1 meter. If the subjective refraction can be performed successfully at 1 meter, a ±0.75 sphere should be subtracted from the 1 meter refraction to make the correction appropriate for the 4 meter distance. This correction should be entered on the Refraction Worksheet in the space provided for distance subjective refraction. (NOTE: Visual acuity will be tested first at the 4 meter distance even if the participant cannot be refracted at this distance.) If the number of letters read correctly at 4 meters is 19 or less, visual acuity must also be tested at 1 meter, in which case the +0.75 sphere should be added to the 4 meter refraction.

2.9 Special situations

Occasionally, one will need to perform refraction and visual acuity on participants with medical or other conditions that make the routine testing difficult, such as Alzheimer's disease or other problems that make strict adherence to the protocol difficult. In such cases one should attempt to follow the protocol as carefully as possible recognizing the special needs of the participant. For example, some participants are unable to concentrate long several lines. It may be necessary to point to letters to get the participant started at the appropriate line or to get them to read letters at all. The goal is to follow the protocol as closely as possible, recognizing that, on occasion, special circumstances may require some minor deviations to get the best estimate of the participant's true best corrected visual acuity.

3. Testing Best Corrected Visual Acuity

3.1 4 meter test

TESTING OF ALL EYES BEGINS AT 4 METERS. First, the right eye is tested with Chart 1, and then the left eye is tested with Chart 2. Each chart should remain hidden from view until the eye in question is ready for testing.

The distance from the participant's eye to the visual acuity chart must be exactly 4.0 meters (13 feet and 1.5 inches, or 157.5 inches). The participant may stand or sit for the 4 meter visual acuity test. If the participant is seated, his or her back should fit firmly touching the back of the chair. The examiner should ensure that the participant is standing or sitting comfortably, that the head does not move forward or backward during the test, and that the participant's eyes remain at the 4 meter distance.

The testing procedure for visual acuity is based on the principle that the objective is to test visual acuity and not intelligence or the ability to concentrate or follow or remember instructions (although all of the factors are involved). The participant should be told that the chart has letters only and no numbers. If the participant forgets this instruction and reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should request a letter in lieu of the number.

The participant should be asked to read slowly (at a rate not faster than about one letter per second) in order to achieve the best identification of each letter and to not proceed until the participant has given a definite response. It may be useful for the examiner to demonstrate the letter-a-second pace by reciting "A, B, C, . . ." If, at any point, the participant reads quickly, he or she should be asked to stop and read slowly. If the participant loses his or her place in reading or the examiner loses his or her place (possibly because the letter are read to quickly), the examiner should ask the participant to go back to where the place was lost. Examiners should never point to the chart or to specific letters on the chart or read any of the letters during the test except for those situations as outlined in Section 2.7.

Each letter is scored as right or wrong (Section 3.3). Once a participant has identified a letter with a definite single-letter response and has read the next letter, a correction of the previous letter cannot be accepted. If the participant changes a response aloud (e.g., "That was a "C", not an "O")

before he or she has read aloud the next letter, then the change should be accepted. If the participant changes a response after beginning to read the next letter, the changes is not accepted.

When the participant says he or she cannot read a letter, he or she should be encouraged to guess. If the participant identifies a letter as one of two or more letters, he or she should be asked to choose one letter and, if necessary, to guess even if the next letter has already been read. The examiner may suggest that the participant turn or shake his or her head in any manner if this improves visual acuity. If the participant does this, care must be taken to insure that the fellow eye remains covered. When it becomes evident that no further meaningful readings can be made, despite urgings to read or guess, the examiner should stop the test for that eye.

There are several reasons for encouraging participants to guess: (1) participants' statements that they cannot identify a letter are often unreliable; (2) encouraging them to guess helps to maximize the participant's effort; (3) it helps to assure uniformity among procedures performed in different clinical centers; and (4) it may help to prevent participant bias (malingering).

3.2 1 meter test

Eyes reading 19 or fewer letters correctly at 4 meters should be tested at 1 meter. If the trial frame is to be removed when changing the test distance from 4 meters to 1 meter, the testing chart (Chart 1 or 2) should first be removed from view to prevent the participant from reading the chart with the fellow eye.

Before testing at 1 meter, a +0.75 sphere should be added to the 4 meter correction already in the trial frame to compensate for the closer testing distance. The participant may stand or sit for the 4 meter test, but must sit for the 1 meter test. (As indicated in Sections 1.5 and 3.1, the participant should be seated comfortably with his or her back firmly placed against the back of the chair.) The avoidance of any head movement forward or backward is particularly important during the 1 meter test. The participant should be asked to read only the first six lines at 1 meter, making 30 the maximum score attainable at that distance (Section 3.3).

After the test of the right eye is completed, occlude the right eye and replace Chart 1 with Chart 2. The test is repeated for the left eye, if indicated by the number of letters read when that eye was tested at 4 meters. When testing of the left eye is completed, Chart 2 should be removed from view. Chart R may be mounted in preparation for the next participant.

3.3 Scoring best corrected visual acuity

The examiner records each letter identified correctly by circling the corresponding letter on the Visual Acuity Worksheet. Letters read incorrectly and letters for which no guesses are made are not marked on the form. Each letter read correctly is scored as one point. The score for each line (which is zero if no letters are read correctly) and the total score for each eye are recorded on the Visual Acuity Worksheet after testing is completed. If testing at 1 meter is not required, 30 points are automatically scored for the 1 meter test. The total combined score (i.e., the sum of the 4 and 1 meter scores) and the approximate Snellen fraction, which is determined based on the lowest line read with one or fewer mistakes, are recorded on the Visual Acuity Worksheet Form.

3.4 Counting fingers, hand motion, light perception, and no light perception

If the participant reads 3 or fewer letters on the 20/800 line at 1 meter, visual acuity is assessed by counting fingers. During this test the examiner holds his or her fingers before the participant's eye good light and the vision is recorded as the furthest distance at which the fingers can be counted. For example, if the participant can accurately count the number of fingers the examiner is holding up from 1 meter (approximately 3 feet) away, this is recorded at counting fingers at 1 meter (approximately 3 feet) on the Visual Acuity Worksheet Form. If the participant cannot distinguish fingers, the examiner should wave a hand in front of the participant's eye. If movements of the hand are perceived by the participants, then the vision is recorded as HM or hand movements.

If visual acuity is so poor that the participant is unable to count fingers or perceive hand motion, light perception should be tested with the indirect ophthalmoscope as the light source. Room lighting should remain at the level of normal visual acuity testing. The subject should close the opposite eye and occlude it by making a tight seal with the palm around the orbit and the bridge of the nose. The indirect ophthalmoscope light should be in focus at 3 feet (approximately 1 meter), the bean should be directed in and out of the eye at least 4 times, and the participant should be asked to respond when he or she sees the light. If the examiner is convinced that the participant perceives the light, vision should be recorded as "light perception"; if not, vision should be recorded as "no light perception."

4. Staff Certification

4.1 Introduction

This section describes the ophthalmic study activities which require certification and the procedures for obtaining and maintaining certification.

It is expected that all ophthalmologists and study personnel will read and become familiar with all aspects of this manual. Study ophthalmologists and Principal Investigators should carefully consider the qualifications of clinical center personnel proposed for certification for the RRR study. Candidates should have experience with basic refraction techniques and the following optical fundamentals:

- Spherical Equivalency
- Plus and Minus Spheres and Cylinders
- Hyperopia, Myopia, and Astigmatism
- "Push Plus" Refraction Principles

4.2 Activities Requiring Certification

Training and certification are required for the following activities:

- ETDRS Refraction
- ETDRS Visual Acuity

In the RRR study, all staff must be fully certified in all study tasks. Full certification in the activities named above must be obtained PRIOR to clinical center staff performing these activities on study participants.

4.3 Forms of Valid Certification

Proof of valid certification (Copy) from Vision Certifying Agency (i.e., Touchstone, EMMES, etc.)

4.4 Study Facilities

The Study Coordinator or other clinical center staff is expected to set up the refraction and visual acuity measurement lane per protocol requirements. If there is a change in the condition or location of the certified examination lane during the course of the study or the office is planning to move, the Study Coordinator is responsible for notifying the sponsor