PROTOCOL

STUDY TITLE:	***E**valuation of **R**e**A**ding **S**peed, Contrast Sensitivity, and Work Productivity in Working Individuals with Diabetic Macular **E**dema Following Treatment with Intravitreal **R**anibizumab (ERASER Study)*
STUDY DRUG	Recombinant humanized anti-VEGF monoclonal antibody fragment (rhuFab V2 [ranibizumab])
SPONSOR	*California Retina Research Foundation* *525 E. Micheltorena Street, Suites A & D* *Santa Barbara, California, United States 93103*
NCT NUMBER:	*NCT02107131*
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DATE:	*12/4/2015*
AMENDMENT:	*3*

1. BACKGROUND

1.1 PATHOPHYSIOLOGY

Diabetic retinopathy is the leading cause of blindness associated with retinal vascular disease. Macular edema is a major cause of central vision loss in patients presenting with diabetic retinopathy. The prevalence of diabetic macular edema after 15 years of known diabetes is approximately 20% in patients with type 1 diabetes mellitus (DM), 25% in patients with type 2 DM who are taking insulin, and 14% in patients with type 2 DM who do not take insulin.

Breakdown of endothelial tight junctions and loss of the blood-retinal barrier between the retinal pigment epithelium and choriocapillaris junction lead to exudation of blood, fluid, and lipid leading to thickening of the retina. When these changes involves or threatens the fovea, there is a higher risk of central vision loss. Functional and eventual structural changes in the blood-retinal barrier as well as reduced retinal blood flow leads to the development of hypoxia. These changes may result in upregulation and release of vascular endothelial growth factor (VEGF), a 45 kD glycoprotein. Vinores and colleagues showed through immunohistochemistical staining, elevated VEGF levels in the retinal neurons and retinal pigment epithelium of patients with diabetic retinopathy. The upregulation of VEGF may further increase retinal edema as VEGF has been shown to be a potent factor increasing retinal vascular permeability.

1.2 TREATMENT

Laser photocoagulation

Focal photocoagulation treatment for diabetic macular edema involves direct treatment of discrete lesions or areas of diffuse leakage in areas surrounding the center of the macula. The aim of focal photocoagulation is to close leaking microaneuryms, intraretinal vascular abnormalities or small neovascular fronds

identified on fluorescein angiography. Grid photocoagulation is applied to areas of retinal thickening or areas of non-perfusion or capillary drop out.

In the Early Treatment of Diabetic Retinopathy Study (ETDRS) and the more recent Diabetic Retinopathy Clinical Research Network (DRCRnet) study, focal photocoagulation of eyes with DME reduced the risk of moderate central vision loss after initiation of treatment. However, a majority of the eyes in each study continued still had macular edema and retinal thickening after one year.

The mechanism of action of focal photocoagulation is not fully understood and the laser energy can cause thermal injury to the retina leading to expanded atrophy larger than the intended laser spot size. This leads to loss of central vision, central scotoma and decreased color vision. Modified treatment parameters and the advent of new lasers have minimized risk of unnecessary thermal injury to the viable retinal tissue.

Other Treatment

Intravitreal steroid medication has been investigated in observational and clinical trials with good outcomes in terms of reduction in macular edema associated with diabetic retinopathy. However, vision threatening side-effects such as increased cataract formation and elevated intraocular pressure were noted in subjects receiving intraocular steroids.

Pars plana vitrectomy has been used to remove vitreomacular traction that may contribute to the existing macular edema in patients with diabetic retinopathy. While this surgical intervention may be effective at reducing macular swelling, the procedure is an invasive intervention with extensive recovery time.

1.3 RANIBIZUMAB AND DIABETIC MACULAR EDEMA

Ranibizumab (rhuFab V2), a monoclonal anti-VEGF antibody fragment that blocks all active isoforms of VEGF-A, is a potent inhibitor of vascular permeability, with the potential to reduce retinal vascular leakage and diminish macular edema. In addition, as an anti-VEGF agent, it may also inhibit neovascularization, a frequent complication of proliferative diabetic retinopathy. Intravitreal use of ranibizumab does carry the risk of intraocular infection, but the risk of glaucoma or cataract formation is lower compared to

triamcinolone use, making it a potentially safer pharmacologic treatment for diabetic macular edema.

1.4 NONCLINICAL EXPERIENCE WITH RANIBIZUMAB

1.4.1 Nonclinical Pharmacokinetics

The pharmacokinetics of ranibizumab have 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 2–3 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 approximately 9 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 01-401E-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 the 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 5000 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 30 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 $\geq$ 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 was 1.9% 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 $\geq$ 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) 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) 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 Objectives

- To determine the mean change in maximum reading speed on MNREAD reading acuity charts (binocular reading) and Radner reading cards (monocular reading) from baseline to Months 3, 6, and 12.

2.2 Secondary Objectives

- To measure the mean change in contrast sensitivity scores on Pelli-Robson charts from baseline to Months 3, 6, and 12.

- To evaluate the mean change in work productivity and activity impairment from baseline to Month 1, Month 3, and Month 12.

- To measure and compare the smallest print size that a subject can resolve on MNREAD reading acuity charts (binocular reading) and Radner reading cards (monocular reading) from baseline to Months 3, 6, and 12.

- To determine the mean change in best-corrected visual acuity in each subgroup, a) monthly treatment group and b) PRN treatment group, on ETDRS visual acuity chart at a starting distance of 4 meters from baseline to Month 12.

- To determine the mean change in central 1mm subfield retinal thickness from baseline to Months 3, 6, and12.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open-label, Phase I/II study of intravitreally administered ranibizumab 0.3mg in subjects with clinical, angiographic, and ocular coherence tomography (OCT) evidence of diabetic retinopathy with associated diabetic macular edema (DME). Patients do not need to be treatment naïve, however there must be a minimum of a 120 day washout in the study eye(s) from any prior intraocular corticosteroids or anti-VEGF treatment. Fourty patients will be enrolled in this study.

Consented, enrolled subjects will be randomized 1:1 to one of two groups a) Monthly treatment group [n=20] or b) as needed treatment group (PRN) [n=20], prior to treatment at the baseline study visit. Each group will receive monthly injections for the first 6 visits. At month 6, the randomized phase of the protocol will begin. This study will enroll 1/2 of subjects with bilateral DME, which will be evenly distributed to the 2 treatment groups (10 subjects in the Monthly group and 10 subjects in the PRN group) to equally assess reading speed and contrast sensitivity with bilateral disease in both groups. All subjects enrolled will be working (at least part time).

All subjects will receive multiple open-label intravitreal injections of 0.3 mg ranibizumab administered every **30** days (±7 days) for 6 injections during the mandatory treatment phase (Day 0, and Months 1, 2, 3, 4, & 5). Subjects in the **monthly treatment group** will continue to receive intravitreal injections of 0.3mg ranibizumab administered every **30** days (±7 days) through 11 months. No study treatment will be administered at the exit visit. Subjects in the **as needed treatment group (PRN)** will receive intravitreal injections of ranibizumab 0.3mg if there is evidence of macular edema on spectral domain optical coherence tomography. In subjects with bilateral DME, both eyes will follow identical treatment regimen (i.e. both eyes will receive monthly dosing if the subject is randomized to monthly treatment group).

All subjects will make monthly visits for 12 months for evaluation of safety and efficacy. All subjects will have their first injection of ranibizumab on Day 0 and may undergo a safety visit one week (±2 days) after the first injection, at the discretion of their study doctor. At subsequent visits, the subject will have a

safety evaluation at the monthly scheduled follow-up visit prior to any intravitreal injection. Subjects will be instructed to contact study personnel after each injection to report any decreased vision, pain or unusual or new ocular symptoms.

3.2 RATIONALE FOR STUDY DESIGN

Treatment of diabetic macular edema (DME) with intravitreal ranibizumab has been shown reduce retinal thickening and improve visual acuity (RIDE/RISE, 2012). However, very few studies have directly assessed the benefits of ranibizumab on patient visual function in eyes with DME. Performance assessment testing including reading speed, contrast sensitivity and work productivity has been used to show functional visual gain in eyes with macular edema secondary to retinal vein occlusion following ranibizumab treatment (Suner, 2013). Thus, performance assessment testing may be a useful tool to evaluate the impact of ranibizumab on day-to-day visual function in patients with DME.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measures

- Change in reading speed (as assessed by number of characters read per minute on MNREAD and Radner reading charts) at Months 3, 6, and Month 12 compared to baseline.

3.3.2 Secondary Outcome Measures

- Change in work productivity (per the WPAI questionnaire - Appendix E) at Months 3, 6, and 12 compared to baseline.
- Best corrected visual acuity (BCVA), as assessed by the number of letters read correctly on the ETDRS eye chart at a starting test distance of 4 meters, at Month 3 and Month 12.
- Incidence and severity of ocular and systemic adverse events, as identified by ophthalmic examination, subject reporting, and physical examination

3.4 SAFETY PLAN

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

All adverse events (serious and nonserious) will be recorded on Case Report Forms (CRFs) for the duration of the study.

The major safety issues concerning administration of ranibizumab are related to the intraocular injection, and include risks of endophthalmitis, retinal break and detachment, cataract formation, intraocular inflammation, intraocular hemorrhage, and intraocular pressure elevation. Previous Phase III clinical trials of anti-VEGF agents using proper sterile technique have demonstrated an extremely low incidence of such events (< 0.2%/per injection)

After each injection of ranibizumab, study staff will confirm patient is at least able to count fingers in each treated eye. Patients may remain at the office for additional time, at the discretion of the treating physician for an intraocular pressure check, or examination of retinal artery perfusion post injection. Following the procedure, subjects will be instructed to use topical antibiotics at the discretion of the treating physician, and to contact the clinic should they experience any symptoms of decreased vision or increasing pain.

The investigator will temporarily withhold further study drug injection for patients experiencing ocular or non-ocular adverse events thought to be related to the drug or its administration. In the event a subject develops an adverse event that is severe in intensity (e.g. endophthalmitis, rhegmatogenous retinal detachment), study discontinuation will be considered for that patient. As with any study of an investigational product, the investigator, patient, or sponsor may request that a subject withdraw from treatment or from the study for safety reasons at any time. Subjects who are discontinued from study treatment may continue to undergo scheduled study visits if they so choose.

The investigators and study sponsors will monitor all adverse events and the FDA will be notified of any interruption in enrollment or change in the conduct of the study.

Given the small number of patients enrolled in this trial, conclusions regarding safety in this subgroup of patients will be limited. However, accumulating data from a number of other trials utilizing intravitreal ranibizumab should provide better estimates of the incidence of various ocular and non-ocular

complications. This information will be monitored by the investigators and information provided to study participants as necessary.

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 (GCPs), and local ethical and legal requirements.

4. MATERIALS AND METHODS

4.1 SUBJECTS

4.1.1 Subject Selection

Describe how subjects in this study will be selected (i.e., who will comprise the study population).

40 subjects from approximately **6** sites in the United States will be enrolled. Eligible subjects will be administered and provided with a copy of informed consent.

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

4.1.2 Inclusion Criteria

Subjects will be eligible 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 18 ≤ years and ability to be employed at the baseline study visit
- Diagnosis of diabetes mellitus (type 1 or 2)
    - Any one of the following will be considered to be sufficient evidence that diabetes is present:
        - Current regular use of insulin for treatment of diabetes
        - Current regular use of oral anti-hyperglycemia agent for the treatment of diabetes

- Clinical evidence of retinal thickening due to macular edema involving the center of the macula, associated with diabetic retinopathy.
- Central diabetic macular edema present on clinical examination or or evidence indicating disease activity on spectral domain OCT.
- Visual acuity score greater than or equal to 19 letters (20/400) and less than or equal to 73 letters (20/40) by the ETDRS visual acuity protocol.
- Media clarity, pupillary dilation and patient cooperation sufficient to allow OCT testing and retinal photography

4.1.3 Exclusion Criteria

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

- Pregnancy (positive pregnancy test) or known to be pregnant; also pre-menopausal women not using adequate contraception.
- Participation in another ocular investigation or trial simultaneously
- Blood pressure > 180/110 (systolic above 180 OR diastolic above 110)
- Any condition that, in the opinion of the investigator, would preclude participation in the study (e.g. chronic alcoholism, drug abuse)
- Evidence of vitreoretinal interface abnormality after ocular exam or OCT that may be contributing to the macular edema
- An eye that, in the investigator's opinion, has no chance of improving in visual acuity following resolution of macular edema (e.g. presence of subretinal fibrosis or geographic atrophy)
- Presence of another ocular condition that may affect the visual acuity or macular edema during the course of the study (e.g. AMD, uveitis, Irvine-Gas)
- Evidence of active neovascularization of the iris or retina
- Evidence of central atrophy or fibrosis in the study eye
- Presence of substantial cataract, one that might decrease the vision by 3 or more lines of vision at any time during the study
- Use of intraocular or periocular corticosteroids in the study eye(s) within 120 days prior to enrollment

- Use of anti-angiogenic drugs in the study eye i.e. pegaptanib sodium, bevacizumab, ranibizumab, aflibercept within 120 days prior to enrollment
- History of vitreous surgery in the study eye
- History of cataract surgery within 3 months of enrollment.
- History of YAG capsulotomy within 2 months of enrollment.
- Visual acuity <20/400 in the fellow eye
- Uncontrolled glaucoma (pressure >30) despite treatment with glaucoma medications.
- History of cerebral vascular accident or myocardial infarction within 3 months prior to Day 0.

4.2 METHOD OF TREATMENT ASSIGNMENT

After informed consent is obtained, screening procedures have been completed and the subject meets all eligibility criteria, all patients will receive treatment with study drug. All patients will receive six consecutive intravitreal injections of 0.3 mg ranibizumab. Subjects in the **monthly treatment group** will continue to receive intravitreal ranibizumab 0.3 mg at each monthly study visit through Month 11. No study treatment is administered at the month 12 visit. Beginning at Month 6, subjects in the **as needed treatment group** will receive additional intravitreal injections of ranibizumab 0.3 mg if there is evidence of disease activity documented on SDOCT scans.

4.3 STUDY TREATMENT

4.3.1 Formulation

0.3-mg dose

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile, 2-mL mL stoppered glass vial. Each single-use vial is designed to deliver 0.05 mL of 6 mg/mL ranibizumab aqueous solution with 10 mM histidine *HCl,* 10%, α-trehalose dihydrate*,* and 0.01% polysorbate *20, pH 5.5.* Each vial contains no preservative and is suitable for **single use only.**

4.3.2 Dosage, Administration, and Storage

a. Dosage

Ranibizumab will be administered to all subjects in a single dose regimen of 0.3 mg every month for the first six months (Day 0, and Months 1, 2, 3, 4, & 5).

Beginning at Month 6, subjects assigned to the **as needed treatment** group will be eligible to receive additional 0.3 mg ranibizumab to treat recurrent macular edema for an additional 6 months. The intent is to administer additional ranibizumab treatment if there is evidence of disease activity documented on SDOCT (e.g., intra-retinal fluid, subretinal fluid and/or cystic changes).

Subjects assigned to the **monthly treatment** group will continue to receive monthly intravitreal injections of 0.3 mg ranibizumab administered every 30 days (±7 days) at each study visit through month 11, for a total of 12 intravitreal injections of 0.3 mg ranibizumab.

b. Administration

**See Appendix B for detailed pre-injection procedures.*

c. 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.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

Subjects may continue to receive all medications and standard treatments administered for their conditions at the discretion of their treating physician. Subjects cannot receive any other anti-VEGF therapy (other than ranibizumab) in either eye.

4.5 STUDY ASSESSMENTS

4.5.1 Assessments during the Treatment Period

All subjects will complete an ophthalmic examination (including intraocular pressure, slit-lamp and indirect ophthalmoscopy), standardized ETDRS vision testing

(monocular then repeat testing under binocular conditions), and spectral-domain OCT testing will be conducted at each monthly visit during the study from Baseline to Month 12 (the OCT model used on a patient must remain consistent throughout the study). At Baseline/Day 0, Months 6 and 12, fundus photographs and fluorescein angiograms will be obtained for all subjects.

All subjects will be administered reading speed tests at baseline, Month 3, Month 6, and Month 12 using the MNREAD reading acuity charts and Radner reading cards (Appendix D). MNREAD reading acuity charts will be administered under binocular conditions. The Radner reading cards will be administered with the subject using one eye at a time. Contrast sensitivity testing using Pelli-Robson charts will be administered to all subjects at baseline, Month 3, Month 6, and Month 12. The Pelli-Robson charts will be viewed monocularly.

The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP) (see Appendix E) will be administered to each subject at baseline, Month 3, Month 6, and Month 12 to assess work productivity and activity impairment due to vision loss associated with diabetic macular edema.

Data will be collected from both eyes including intraocular pressure, ETDRS vision testing, and spectral-domain OCT testing. All testing will be done prior to administration of intravitreal injections.

4.5.2 Early Termination Assessments

Subjects who withdraw from the study prior to completion should return for an early termination evaluation within **30** days (±**7** days) following the last injection/study visit for monitoring of all adverse events (serious and nonserious).

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 of the following reasons: if it is in the best interest of the subject, intercurrent illness, adverse events, or

worsening condition. The California Retina Research Foundation or Nathan Steinle, MD 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 may re-enter the study at the discretion of the study doctor.

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

- 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
- 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

This study may be terminated by California Retina Research Foundation or Genentech 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

There is no formal sample size calculation in this exploratory pharmacokinetic study. As this is a pilot study, a sample size of **40** patients is chosen, making

sure that it is feasible to conduct the study and logistically to complete the study within 1-2 years.

4.8.2 Safety Analyses

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 pilot study.

4.8.3 Efficacy Analyses

There is no formal sample size calculation in this exploratory analysis of intraocular fluid, serum and plasma samples. A sample size of **40** patients was chosen, making sure that it is feasible logistically to conduct and to complete the study within two years.

a. Primary Endpoint

The primary endpoint is the mean change in maximum reading speed from baseline to Months 3, 6, and 12, based on MNREAD reading acuity charts (binocular reading) and Radner reading cards (monocular reading).

b. Secondary Endpoints

The secondary endpoints include the following:

- Mean change in work productivity from baseline (per the WPAI:SH questionnaire) to Months 3, 6, an 12.
- Mean change in contrast sensitivity from baseline to Months 3, 6, and 12 based on Pelli-Robson charts
- Mean change in best-corrected visual acuity from baseline to Month 12 based on ETDRS visual acuity charts.
- Mean change in central 1mm subfield thickness from baseline to Months 3, 6, and Month 12.

4.8.4 Missing Data

Analyses will be done two ways: one including all subjects who were enrolled and one only including subjects that were not discontinued and did not miss 2 or more visits in a row or 3 visits total will be assessed. 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.

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APPENDIX A

	Assessments During Treatment Period						Randomized Treatment Period						
Study Flowchart	Screen/Day 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Informed Consent	X												
Vital Signs	X												
Weight/Height	X												
Ocular History	X												
WPAI:SHP	X			X			X						X
Refraction[b]	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
BCVA (4m starting distance; monocular then repeat binocular)	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect Ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus Photos	X						X						X
FA	X						X						X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular Pressure	X	X	X	X	X	X	X	X	X	X	X	X	X
MNREAD (binocular)	X			X			X						X
Radner	X			X			X						X
Pelli-Robson	X			X			X						X
Ranibizumab 0.3mg	X	X	X	X	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	

[a]Subjects assigned to as needed treatment group will receive intravitreal ranibizumab 0.3mg if macular edema is present on SDOCT. Subjects assigned to monthly treatment group will receive intravitreal ranibizumab 0.3mg.
[b]Refraction required only at baseline, and visits where BCVA decreases by 10 or more letters