PROTOCOL

STUDY TITLE:	The effect of visual acuity and hard exudate resolution in the treatment of diabetic macular edema with center involved edema and lipid exudates. Phase I/II
STUDY DRUG	Recombinant humanized anti-VEGF monoclonal antibody fragment (rhuFab V2 [ranibizumab]) 0.3mg Lucentis
SPONSOR	South Coast Retina Center; Carson, McBeath, Boswell Inc. 4300 Long Beach Blvd Ste 300, Long Beach CA 90607
IND:	*Insert IND Number*
INVESTIGATOR	Julie Gasperini, MD
SUB-INVESTIGATORS	*Michael Roh, MD; John McBeath, MD; Tom O'heam MD*
DATE FINAL:	*December 1st, 2014*
AMENDMENT :	

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1. BACKGROUND

1.1 PATHOPHYSIOLOGY

Diabetes mellitus affects over 350 million people worldwide and diabetic retinopathy is the most common microvascular complication of diabetes. Diabetic macular edema (DME) is the leading cause of vision loss in patients with diabetes and affects 30% of patients who have had diabetes for at least 20 years. In DME, the disruption of the blood-retinal barrier results in accumulation of fluid in the neurosensory retina and the formation of lipid-rich extravascular deposits known as hard exudate, resulting in loss of central vision. Deposits of hard exudate near the fovea are thought to be associated with an increased risk of vision loss.

The pathophysiology that results in the microvascular damage in DME includes the direct toxic effects of hyperglycemia, sustained alterations in cell signaling pathways, and chronic microvascular inflammation with leukocyte-mediated injury. Chronic retinal microvascular damage results in elevation of intraocular levels of vascular endothelial growth factor A (VEGF). VEGF levels correlate with the breakdown of the blood retinal barrier and are significantly elevated in the eyes with exudative retinal disease such as DME. VEGF mediates many important physiologic processes and results in vascular hyperpermeability causing leakage of intraretinal fluid resulting in macular edema. Anti-VEGF drugs reduce DME by decreasing vascular permeability.

1.2 TREATMENT OF DIABETIC MACULAR EDEMA

The historic standard of care for DME was macular laser photocoagulation. Multiple studies have now demonstrated that anti-VEGF therapy is more effective than laser alone for vision gain and avoiding vision loss in patients with center-involved DME, and avoids the ocular side effects associated with laser treatment. Anti-VEGF agents such as ranibizumab, bevacizumab, aflibercept, have become the preferred treatment option for the management of diabetic macular edema in many patients.

Studies such as RISE/RIDE demonstrated that intravitreal ranibizumab was superior to laser alone. The BOLT study demonstrated that intravitreal bevacizumab was superior to laser alone. DRCR protocol I demonstrated that intravitreal ranibizumab with either prompt or deferred laser provided superior anatomic and functional outcome in individuals with DME through 2 years compared with the previous gold standard of laser alone and steroids did not have a similar affect.

1.3 RANIBIZUMAB AND LIPID AND HARD EXUDATES

Ranibizumab is a humanized monoclonal antibody fragment that binds and inhibits VEGF-A. Multiple studies have clearly demonstrated that ranibizumab is superior to laser alone for vision gain and avoiding vision loss in patients with center involved diabetic macular edema. Ranibizumab is FDA approved for the treatment of diabetic macular edema in the dose of 0.3mg.

Deposits of lipid exudates near the fovea are thought to be associated with an increased risk of vision loss in DME. The RIDE/RISE hard exudate retrospective analysis found that hard exudates were present in 75% of patients at baseline, ranibizumab significantly reduces the area of hard exudate over time compared to sham, especially in those graded as moderate exudate, but the effect is gradual with a detectable affect no earlier than 6 months (as opposed to the rapid improvement in macular edema) and the difference between treatment groups became evident at 12 months. At baseline, there was no correlation between visual acuity and the presence of hard exudate in the central subfield in any treatment arm. Post-baseline, there was no consistent correlation between presence of HE in the central subfield and VA change over time.

Since ranibizumab has been shown to be an effective treatment for both center involved diabetic macular edema and for resolving lipid exudates, the rationale of this study is to prospectively determine if continued treatment with intravitreal anti-VEGF (ranibizumab) until both center-involved macular edema AND lipid exudates resolve will impact final visual acuity. The secondary outcomes would evaluate ranibizumab's effect on lipid exudate resolution at the fovea and macula.

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 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 7-8 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 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 serious 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) 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 non-serious 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 iridocylitis 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

To evaluate the effect of intravitreal ranibizumab 0.3mg on visual acuity and hard exudate resolution in the treatment of diabetic macular edema with lipid exudates in the central subfield. This group is at high risk of deposition of lipid in the fovea and vision loss. The patients would be randomized to 1 of 2 groups. Group 1 would be treated with intravitreal ranibizumab 0.3mg until the macular edema is resolved based on the DRCR protocol I 4:2:7 strategy. The definition of success would be changed for Group 2 and treatment would continue until the lipid exudates in the central subfield also resolve.

2.1 Primary Objective

The primary objective of this study is to evaluate the effect of intravitreal ranibizumab 0.3mg on visual acuity in the treatment of center involved diabetic macular edema with lipid exudates in the central subfield.

2.2 Secondary Objectives

The secondary objective of this study is to evaluate the effect of intravitreal ranibizumab 0.3mg on lipid clearing in the central subfield and throughout the macular grid in patients with center involved diabetic macular edema with lipid exudates in the central subfield.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open-label, Phase I / II study of intravitreally administered 0.3mg ranibizumab in subjects with diabetic macular edema and lipid exudates in the central subfield.

Consented, enrolled subjects will receive multiple open-label intravitreal injections of 0.3 mg ranibizumab administered every 30 days for 12 months per the treatment algorithm.

The patients will be randomized to 1 of 2 treatment groups.

- Group 1: Treatment algorithm based on the DRCR protocol I 4:2:7 strategy based on the presence of macular edema.
- Group 2: Continue treatment until not only the macular edema is resolved but also until the lipid exudate is resolved.

Sample size: 30 eyes

Follow-up Schedule: Every 4 weeks throughout the study.

3.2 RATIONALE FOR STUDY DESIGN

DRCR Protocol I 4:2:7 strategy for Group 1

Prior to the 16-week study visit, treatment study drug was given every 4 weeks regardless of the visual acuity or optical coherence tomography (OCT) central subfield thickness.

At the 16 and 20 week study visits, study drug was required monthly unless 'success' criteria (defined as visual acuity letter score ≥84 (20/20) or OCT central subfield thickness <300;, in which case study drug injection was at investigator discretion.

At each visit from 24 to 48 weeks, eyes were categorized as meeting either 'success' as defined above, 'improvement', 'no improvement', or 'failure'. Improvement required a study drug injection. If an eye was categorized as 'no improvement' because it met neither the criteria for 'success' or 'improvement', but had not yet met the criteria for 'failure' a study drug injection could be given at investigator discretion. Eyes that met 'failure' criteria could be treated at investigator discretion with study drug injection or exited from the study.

Definitions:

- Improvement: either visual acuity improved by ≥5 letters or OCT central subfield thickness improved by ≥10% since the last injection

- No improvement: Success and failure/futility criteria not met and visual acuity letter score improved by <5 letters (or worsened) and OCT central subfield thickness decreased by <10% (or increased) since the last injection
- Failure: Visual acuity 10 or more letters worse than baseline, OCT central subfield thickness ≥300 um, DME judged to be the cause of visual acuity loss
- Futility: After 52 week visit: OCT central subfield ≥300 um, DME judged to be the cause of visual acuity loss

For Group 2 the treatment algorithm definition of 'success' would change to also include resolution of lipid exudate. So even if the macular edema has resolved, treatment with study drug injection would continue until the lipid exudate in the central subfield was resolved.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measures

Compare Group 1 and Group 2 for Best correct 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, over 6 and 12 months

3.3.2 Secondary Outcome Measures

1. Lipid clearing in the central subfield.
    - % of patients with improvements in lipid deposits at 6 and 12 months
    - % of patients with complete resolution at 6 and 12 months
    - Time to complete resolution (Group 1 compared with Group 2)

2. Lipid clearing throughout the macular grid.
    - % of patients with improvements in lipid deposits at 6 and 12 months
    - % of patients with complete resolution at 6 and 12 months
    - Time to complete resolution (Group 1 compared with Group 2)

3. Measures for safety and tolerability are the following:
    - Incidence and severity of ocular adverse events, as identified by eye examination (including visual acuity testing)

- Incidence and severity of other adverse events, as identified by physical examination, subject reporting, and changes in vital signs

The reading center (Doheny Image Reading Center- Srini Vas Sadda, MD) will develop severity standards and a grading scale for the lipid exudates based on OCT and fundus photography.

3.4 SAFETY PLAN

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

Injection-related: endophthalmitis, retinal detachment, retinal tears, cataract, intraocular hemorrhage, increased intraocular pressure.□

Ocular drug-related: inflammation, cataract, cataract surgery, increased intraocular pressure, glaucoma medications, glaucoma surgery, new or worsening traction retinal detachment.

Systemic drug-related: hypertension, cardiovascular events, and cerebrovascular events.

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

30 subjects from 2 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
- Type 1 or Type 2 Diabetes mellitus
- Best corrected ETDRS visual acuity (20/32–20/320) or letter score 78 to 24
- Diabetic macular edema on clinical examination involving the center of the macula assessed to be the main cause of visual loss
- Retinal thickness measured on spectral domain optical coherence tomography (OCT). Zeiss Cirrus: ≥290μm in women and ≥305 μm in men in the central subfield. Heidelberg Spectralis: ≥305μm in women and ≥320 μm in men in the central subfield
- Lipid exudates involving the central subfield on spectral domain OCT.

4.1.3 Exclusion Criteria

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

- Treatment for diabetic macular edema within the prior 4 months.
- Panretinal photocoagulation within the prior 4 months or anticipated need for panretinal photocoagulation within the next 6 months
- major ocular surgery within the prior 4 months
- myocardial infarction, other cardiac event requiring hospitalization, cerebrovascular accident, transient ischemic attack, or treatment for acute congestive heart failure occurred within 4 months before randomization
- Pregnancy (positive pregnancy test) or lactation
- Premenopausal women not using adequate contraception. The following are considered effective means of contraception: surgical sterilization or 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 another simultaneous medical investigation or trial

4.2 METHOD OF TREATMENT ASSIGNMENT

Patients will be randomized to either treatment group 1 or 2 via a computer generated randomization schedule. Since this is a small study, to control and balance the influence of covariates, patients with visual acuity of less than 20/80 or better than 20/80 will be equally randomized to Group 1 or 2.

Given that this is a small study, subjects that are exited with less than 6 months of data can be replaced.

4.3 STUDY TREATMENT

4.3.1 Formulation

0.3-mg Lucentis:

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.**

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

4.3.2 Dosage, Administration, and Storage

a. **Dosage:** Ranibizumab 0.3mg

b. **Administration:**

Intravitreal Ranibizumab 0.3mg with follow-up visits every 4 weeks.

The patients will be randomized to 1 of 2 treatment groups.

- **Group 1:** Treatment algorithm based on the DRCR protocol I 4:2:7 strategy based on the presence of macular edema.
- **Group 2:** Continue treatment until not only the macular edema is resolved but also until the lipid exudate is resolved.

DRCR Protocol I 4:2:7 strategy for Group 1

Prior to the 16-week study visit, treatment study drug was given every 4 weeks regardless of the visual acuity or optical coherence tomography (OCT) central subfield thickness.

At the 16 and 20 week study visits, study drug was required monthly unless 'success' criteria (defined as visual acuity letter score ≥84 (20/20) or OCT central subfield

thickness <300;, in which case study drug injection was at investigator discretion.

At each visit from 24 to 48 weeks, eyes were categorized as meeting either 'success' as defined above, 'improvement', 'no improvement', or 'failure'. Improvement required a study drug injection. If an eye was categorized as 'no improvement' because it met neither the criteria for 'success' or 'improvement', but had not yet met the criteria for 'failure' a sham or study drug injection could be given at investigator discretion. Eyes that met 'failure' criteria could be treated at investigator discretion with study drug injection or exited from the study.

Improvement: either visual acuity improved by ≥5 letters or OCT central subfield thickness improved by ≥10% since the last injection

No improvement: Success and failure/futility criteria not met and visual acuity letter score improved by <5 letters (or worsened) and OCT central subfield thickness decreased by <10% (or increased) since the last injection

Failure: Visual acuity 10 or more letters worse than baseline, OCT central subfield thickness ≥300 um, DME judged to be the cause of visual acuity loss

Futility: After 52 week visit: OCT central subfield ≥300 um, DME judged to be the cause of visual acuity loss

For Group 2 the treatment algorithm definition of 'success' would change to also include resolution of lipid exudate. So even if the macular edema was resolved, treatment with study drug injection would continue until the lipid exudate in the central subfield was resolved.

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

c. <u>Storage</u>

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.

Lucentis will be provided for the fellow non-study eye if treatment is indicated.

4.5 STUDY ASSESSMENTS

4.5.1 Assessments during the Treatment Period

Visit Schedule: Every 4 weeks (+/- 1 week) for 12 months. If an injection is administered on visit 12, a follow-up visit will be performed 4 weeks later to assess for adverse events and treatment response. If the investigator chooses to see the participant more frequently as part of usual care or a participant experiences visual acuity loss requiring earlier follow-up, limited data will be collected at those visits.

Testing Procedures: A history will be elicited from the subject and extracted from available medical records at enrollment. Data to be collected may include: age, gender, ethnicity and race, diabetes history and current management, other medical conditions, as well as ocular diseases, surgeries, and treatment.

The following procedures will be performed at each protocol visit unless otherwise specified.

1) OCT will be performed at each visit. Fundus Photography (FP) on the study eye(s) at baseline and month 3, 6, 9, and 12. If lipids/ exudates resolve at an in-between visit, FP will also be performed at that time. A reading center will review the images at baseline and month 3, 6, 9, 12, and a lipid resolution visit if indicated.

2) Fluorescein angiogram of both eyes at Visit 0 and 12

3) Ocular exam in the study eye(s), including slit lamp examination, lens assessment, measurement of intraocular pressure and dilated ophthalmoscopy

4) Measurement of blood pressure (enrollment only)

5) Best Corrected ETDRS visual acuity testing at 4 meters the study eye and both eyes at visit 0 and 12.

If fundus photography or fluorescein angiogram were performed (using the study technique and by study certified personnel) as part of usual care within 4 weeks of randomization, it does not need to be repeated specifically for the study.

OCT, fluorescein angiogram, and fundus photography will all be sent to a reading center for manual grading. Study participant eligibility is determined by the site (i.e., individuals deemed eligible by the investigator will be randomized without pre-randomization reading center confirmation). The reading center will create a grading scale for the lipid exudate in the center subfield and macular grid.

Delay in giving injections: If a scheduled injection is not given by the end of the visit window, it can still be given late.

Non-Study Eye Injections: if the non-study eye is going to be treated for any condition which requires treatment with an anti-VEGF agent, study provided ranibizumab must be used. However, if intravitreal anti-VEGF treatment is planned on the same day as an intravitreal injection in the study eye, the study eye will be injected first, followed by the non-study eye. If a different intravitreal anti-VEGF injection than described above is desired in the non-study eye, a discussion with the PI is required first.

4.5.2 Early Termination Assessments

Subjects who withdraw from the study prior to completion should return for an early termination evaluation 30 days (±7days) following the last injection/study visit for monitoring of all adverse events (serious and non-serious). The schedule of assessments for early termination is the same as that for the final visit.

4.5.3 Reading Center

Summary of Reading Center Grading Plan for Lipid Associated With Diabetic Macular Edema

a. Image acquisition

The reading center will provide written image acquisition manuals for all photographic procedures relevant to this IST. In particular for obtaining stereo color fundus photographs and spectral domain OCT images. These procedure manuals will include a description of image transmittal methods. A project manager will be assigned at the reading center who will interact with the clinical site personnel. Feedback will be provided on an on-going basis through the course of the study regarding the quality of images and compliance with protocols. The reading center will not perform an a priori certification of instruments or operators for this protocol.

b. Summary of grading strategy

All grading will be performed by a experienced, trained grader who has been certified for diabetic retinopathy grading. This study will employ a single masked grading workflow, but a percentage of cases will be re-graded to confirm reproducibility. The initial set of submissions will also be reviewed by the reading

center principal investigator (Sadda), as will any questionable or difficult cases (as determined by the 1st grader) during the course of the study. Grading results will be entered into a study database or spreadsheet and will be provided the IST PI or Genentech for analysis. All grading will be completed within 2 weeks of receipt of the image data, assuming there are no problems with the image submission.

c. Lipid Grading Methodology Overview

1. Color Fundus Images

Grading of lipid/ hard exudates on color fundus photographs has been defined in previous large clinical trials (specially the ETDRS). We propose to use a similar protocol, which will facilitate comparisons with historical data.

Specifically, severity and extent of lipid exudates will be determined by comparison of subject color photos to ETDRS reference standards in accordance with the ETDRS scale below (Excerpt from Reading Center central grading protocol):

Presence/Severity of Hard Exudates

Identification of hard exudates is described in Section 4.2.1.7.

When using standard photographs, the grading of hard exudates is based on the area of retina involved in comparison.

The following scale adapted from the ETDRS grading protocol[1] is used to evaluate hard exudates:

Grading Scale	*Findings observed on Colors in Fields 2 – 7*
0	No hard exudate
1	Questionable hard exudate
2	Definite hard exudate < Std Photo #3*
3*	Hard exudate ≥ Std Photo #3* but < Std Photo #5*
4*	Hard exudate ≥ Std Photo #5* but < Std Photo #4*
5*	Hard exudate ≥ Std Photo #4*
8	Cannot Grade

** Standard Photographs 3, 4, and 5 are not required in determining the severity level of DR and will not be used unless otherwise specified in a study specific grading protocol.*
** Grades 3, 4, and 5 will not be used unless otherwise specified in a study specific grading protocol.*

2. Spectral Domain OCT

Volume SD-OCT acquisitions (512x128 over a 6x6 mm square centered on the fovea) will be obtained for both eyes in each case, though only the study eye will be graded here. Lipid or hard exudates are recognized or defined on OCT to be discrete areas of increased hyper-reflectivity within the neurosensory retina associated with optical shadowing below. Lipid severity will be assessed by one or both of two methods: (1) computation of actual lipid volume based on manual segmentation of dense volume scans (this is a time-consuming, but precise method), (2) semi-quantitative determination of lipid severity within sections of a detailed (16 square grid). These two metrics will be correlated with one another. If the semi-quantitative method proves effective (i.e. correlates well with the precise volume), this may be the preferred approach.

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, intercurrent illness, adverse events, or worsening condition. The **South Coast Retina Center** or Julie Gasperini MD (PI) 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

This study may be terminated by **South Coast Retina Center** 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 a pilot/phase I or pharmacokinetic/pharmacodynamics study. As this is a phase I/II study, a sample size of **30** patients is chosen, making sure that it is feasible financially to conduct the study and logistically to complete the study within **2** year / years.

If and when the study is planned for a phase II/III randomized control trial, appropriate statistical analysis will be determined.

4.8.2 Safety Analyses

Any adverse events, laboratory assessments, physical examinations, vital signs, ocular examinations and measurements from all **30** subjects will be utilized to summarize safety data for this pilot study.

4.8.3 Efficacy Analyses

a. Primary Endpoint

Best correct 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 6 and 12.

c. Secondary Endpoints

1. Lipid clearing in the central subfield:
    - % of patients with improvements in lipid deposits at 6 and 12 months
    - % of patients with complete resolution at 6 and 12 months

2. Lipid clearing throughout the macular grid:
    - % of patients with improvements in lipid deposits at 6 and 12 months
    - % of patients with complete resolution at 6 and 12 months

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 ranibizumab, 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 [diabetic macular edema] that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

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 SERIOUS ADVERSE EVENTS

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

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., 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.
- It results in persistent or significant disability/incapacity (i.e., 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 (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

5.3 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).

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 [or "initiation of any non-standard of care study procedures"] and ends 30 days [or insert other time period] 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.

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 (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the {study drug} (see following guidance), and actions taken.

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

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the {study drug 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 {study drug}; and/or the AE abates or resolves upon discontinuation of the {study drug} or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the {study drug} (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to {study drug} 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.

5.4 EVALUATIONS

Reviews of body systems will be performed.

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

5.5 VITAL SIGNS

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

5.6 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

5.6.1 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?"

5.6.2 Specific Instructions for Recording Adverse Events

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

a. 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, asterisks, 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.

b. 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".

c. 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").

d. 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.

e. 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.

f. 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.

g. 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.

h. 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 Product

Lucentis Events of Special Interest are:

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

i. 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.
- Serious AE reports that are related to the ranibizumab and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the ranibizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

Additional Reporting Requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with the [study drug ranibizumab] will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech.

Note: Investigators should also report events to their IRB as required.

5.6.3 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient 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

5.6.4 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 patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient 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 patient 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

5.6.5 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 [study drug ranibizumab]. An unexpected adverse event is one that is not already described in the [study drug 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 [study drug ranibizumab]. An unexpected adverse event is one that is not already described in the [study drug 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

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:

Western Institutional Review Board□

1019 39th Avenue SE Suite 120□Puyallup, WA 98374-2115

Office (360) 252-2500, (800)562-4789

Fax (360) 252-2498

Email: clientservices@wirb.com

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

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 mailed to the assigned contact for the study: lucentisgsr_coa-d@gene.com , SRT fax number 866-728-4622

5.6.6 SAFETY REPORTING FAX COVER SHEET

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	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient 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

6.0 INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study, the following documents must be on file with **South Coast Retina Center** or its appointed representative:

- FDA correspondence letter assigning an IND number or an IND waiver letter
- Original U.S. FDA Form 1571 (if applicable)
- Original U.S. FDA Form 1572 (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator (if applicable)
- The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae of the Principal Investigator
- Medical License
- Written documentation of IRB approval of the protocol (identified by **[South Coast Retina Center]**, protocol number or title and date of approval)
- IRB Approved protocol
- Fully executed contract
- Documentation of registration into clinical research website (e.g., www.clinicaltrials.gov) (as applicable)
- Investigator Brochure Signature Receipt

6.2 STUDY COMPLETION

The following data and materials are required by **[South Coast Retina Center]** before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period (if applicable)
- Case Report Forms properly completed by appropriate study personnel and signed and dated by the investigator (if applicable)

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

6.3 INFORMED CONSENT

Informed consent documents will be provided to each subject.

The informed consent document must be signed and dated by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The following basic elements must be included:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures or drug used for purposes which are experimental
- A description of any reasonably foreseeable risks or discomforts to the patients
- A description of any benefits to the patient or to others which may reasonably be expected from the research. A description that there may be no benefit from this research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality records identifying the patient will be maintained and that notes the

possibility that the FDA and the **South Coast Retina Center** and the drug manufacturer may inspect the records

- For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available should injury occur and, if so, what they consist of or where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and research patient's rights, and whom to contact in the event of a research-related injury to the patient
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

6.4 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 **South Coast Retina Center** (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.5 CASE REPORT FORMS

All CRFs should be filled out completely by appropriate personnel. The CRF should be reviewed, signed, and dated by the investigator.

All CRFs should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced CRF copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID ON THE ORIGINAL.

6.6 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.

6.7 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.

6.8 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 CRFs, 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.

6.9 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 email: lucentisgsr_coa-d@gene.com,
Fax: 866-728-4622

REFERENCES

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13. *List references alphabetically, and format them using the Vancouver style described below.*

APPENDIX A
Study Flowchart

	Pretreatment	Assessments During Treatment			Other Assessments	
	Screen[a]	Randomization / Visit 0[a]	Visits 1-11[b]	Visit 12[b]	Visit 13[b]	Lipid Resolution Visit (if not on a visit where FP is scheduled)
Informed consent	x	x				
Demographic data		x				
ETDRS best corrected visual acuity [c]		x	x	x	x	
Eye Exam [d]		x	x	x		
Medical History & Blood pressure		x				
Fundus Photography (FP)		x	Month 3, 6, 9 12	x	x	x
SD-OCT		x	x	x	x	
Fluorescein Angiogram		x		x		
Ranibizumab treatment [e]		x	x	x		
SAE monitoring		x	x	x	x	

[a] The screening and randomization visit (visit 0) can be on the same day..

[b] All visits are every 4weeks (+/-1 week) for 1 year, if an injection is administered at visit 12, then a follow up exam will occur 4 weeks later (visit 13) to assess AEs and therapeutic response.

[c] Includes refraction in both eyes on visit 0 and 12 and in the study eye on all other study visits unless treatment is given in the non study eye

[d] Eye Exam includes slit lamp exam (including assessment of lens), measurement of intraocular pressure, and dilated ophthalmoscopy.

[e] Ranibizumab treatment is administered per the protocol

APPENDIX B
Pre-Injection Procedures for All Subjects

The following procedures will be implemented to minimize the risk of potential adverse events associated with serial intravitreal injections (e.g., endophthalmitis). Aseptic technique will be observed by clinic staff 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 intravitreal injection procedure will follow the DRCR.net non-protocol specific injection procedure.

The Diabetic Retinopathy Clinical Research Network Non Protocol–Specific Injection Procedure

A. Intravitreal Injection Procedure

NOTE: If an injection is to be given in the non-study eye at the same visit as a study eye injection, all required injection procedures described below must be completed in the study eye prior to initiating any pre-injection preparation of the non-study eye. In addition, the drug to be used in the non-study eye should not be present in the room prior to completion of all study eye injection procedures. All required injection procedures listed below must be performed on the non-study eye.

1. Pre-Injection

a. On the day of injection, topical antibiotic drops may be administered at the discretion of the investigator as part of standard care, but are not required as part of a study procedure.

b. The treating investigator and a second person should confirm which is the study eye to receive the intravitreal injection (if applicable) while directly viewing a computer screen with this information or a print out of a computer screen with this information that indicates the study eye and with this information at hand, mark that eye (with a sticker or marking pen) above the corresponding eyebrow.

c. Two individuals (the injecting ophthalmologist and another individual e.g. the coordinator) must confirm the study drug number from the vial obtained from the refrigerator (if applicable) with a print out from the website or while directly viewing a computer screen with this information prior to injection to ensure accuracy.

d. When the study participant is ready for the injection, apply at least one drop of topical anesthetic (solution or gel) to the eye.

e. The eye then will be prepared for injection using the following sequence of steps:

1. Consider placing 2-3 drops of 5% povidone iodine in the lower fornix and/or using sterile cotton-tipped applicators soaked in 5% or 10% povidone iodine to swab the upper and lower eyelid margins and the upper and lower eyelashes (Optional).
2. Place a sterile eyelid speculum to stabilize the eyelids.□Consider additional anesthesia with the application of one or two cotton- tipped applicators soaked in topical anesthetic over the intended injection site for at least 30 seconds. A subconjunctival anesthetic can be used if the investigator believes that topical anesthetic is not sufficient to minimize discomfort. Protocol Chair approval is required for use of retrobulbar anesthetic. The use of lidocaine gel or other types of viscous anesthetic (e.g. TetraViscTM) is permitted.
3. Encourage the study participant to look superonasally during the application of povidone iodine. Apply one of the following to the conjunctiva directly over and surrounding the intended injection site:
    a. A cotton-tipped applicator soaked in 5% or 10% povidone iodine
    b. A 10% povidone iodine Swabstick
    c. At least 1-3 drops of 5% povidone iodine (at least enough to cover the intended injection site)
4. Allow 30-60 seconds for the povidone iodine to be in contact with the injection site before injection.

NOTE: As indicated above, injection preparation must include the use of povidone-iodine either applied directly to the injection site using topical drops, a cotton-tipped applicator, or swabstick. If a study participant experiences an adverse reaction to povidone-iodine, other approaches to limit the exposure of povidone-iodine may be permitted. However, a DRCR.net study participant may not receive a study intravitreal injection without use of povidone-iodine directly to the injection site just prior to the injection.

Examples of approaches that may be used in study participants with prior adverse reactions associated with povidone-iodine include using a limited amount of povidone-iodine by placing a swab directly on the injection site after the lid speculum has been placed, subsequently ensuring that nothing further touches that site before the injection. Alternatively, investigators could consider using povidone-iodine and then gently irrigating the eye with sterile saline after the injection to try to rinse away any remaining povidone-iodine. In the extremely rare circumstance, if the study participant is perceived likely to have a severe adverse reaction associated with povidone-iodine and an alternative approach such as those discussed above is not viable, study intravitreal injection cannot be given at that study visit and the investigator should discuss the circumstance with the Protocol Chair or other investigator as designated by the Coordinating Center.

2. Injection

a. The position of the injection site is located at 3.0mm-4.0mm posterior to the limbus.

b. The surgeon prepares the proper volume of drug to be injected by drawing 0.2mL into the syringe using the sterile 19-gauge filtered needle provided. The 19-gauge needle should then be removed and the sterile 30-gauge needle provided should be placed onto the syringe. A 32-gauge needle may be used in place of the provided 30-gauge needle, if preferred. With the needle cap removed, fluid is expelled at an approximately 45-degree angle until the plunger is advanced to 50 µL (0.05 mL). The syringe is now ready for injection.

c. Inject the drug into the vitreous cavity pointing toward the optic nerve via the pars plana.

3. Post-Injection

a. Remove the lid speculum and avoid any excess pressure on the eye.
b. Assess for any complications either via indirect ophthalmoscopy to confirm that the central retinal artery is perfused (even if it is pulsating) or a vision check to confirm that there is some perception of vision in the study eye (for example, able to count fingers or perceive hand motion or light perception).
c. At the discretion of the investigator topical antibiotic drops or ointment supplied as part of standard care but not part of the study may be provided to the study participant and used QID for 3 days (inclusive of the day of injection).

NOTE if indirect ophthalmoscopy is checked it should be recorded. If the IOP is checked multiple times, the last IOP taken before the study participant leaves the physician's office should be recorded.

APPENDIX C

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.

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

MCN	Reported Event	Submission Date

OR

2. 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, the PI selects one of the following boilerplate conclusion statements, if applicable. The PI may also craft an alternative conclusion.

1. Based on review of available data, **South Coast Retina Center** 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

2. Based on review of available data, the **South Coast Retina Center** 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

3. Based on review of available data, the **South Coast Retina Center** 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 **South Coast Retina Center** does not believe that changes to the conduct of this clinical trial are warranted. *This statement can be modified if changes to the conduct of the clinical trial are made.*