PROTOCOL

STUDY TITLE:	A phase I/II, open-label, multicenter, randomized, controlled study of the safety, tolerability and efficacy of intravitreal injections of 0.3 mg ranibizumab given monthly compared to a Treat and Extend protocol, with and without laser photocoagulation, in patients with Diabetic Macular Edema (T-REX-DME)
STUDY DRUG	Recombinant humanized anti-VEGF monoclonal antibody fragment (rhuFab V2 [ranibizumab])
SPONSOR	Palmetto Retina Center 124 Sunset Court West Columbia, SC 29169
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1. BACKGROUND

1.1 PATHOPHYSIOLOGY

Diabetes mellitus continues to be a tremendous health burden in America. In 2007, the prevalence of diabetes was estimated to 23.6 million people, or 7.8% of the US population (Center for Disease Control and Prevention, 2007). Diabetic retinopathy is the leading cause of blindness among working age adults, accounting for 8% of all legal blindness (Klein and Klein, 1995; Yau et al, 2012). During the first two decades with the disease, nearly all of those with type 1 diabetes and > 60% of those with type 2 diabetes have some degree of retinopathy (Fong et al, 2003). The International Diabetes Federation estimates that 285 million individuals worldwide have diabetes mellitus and that approximately 14% of this group has diabetic macular edema (International Diabetes Federation; 2012).

The risk factors for retinopathy progression of retinopathy are not completely understood. Age, race, and duration of diabetes all appear to play a role. Other factors, such as poor glycemic and blood pressure control, are associated with retinopathy progression as well (ACCORD Eye Study Group, 2010).

Three forms of retinopathy are commonly recognized in association with all forms of diabetes mellitus: 1) non-proliferative diabetic retinopathy (NPDR), 2) PDR, and 3) DME.

NPDR is characterized by ophthalmoscopically visible abnormalities that include microaneurysms, intraretinal hemorrhages, exudates, retinal nerve fiber layer infarcts called cotton wool spots, and, in more severe cases, venous beading and intraretinal microvascular abnormalities. Over time, NPDR may progress to more severe PDR, the hallmark of which is neovascularization on the surface of the retina, optic disc, iris, or anterior chamber angle. PDR is associated with a high risk of visual morbidity arising from vitreous hemorrhage, traction retinal detachment, and neovascular glaucoma (Diabetic Retinopathy Study [DRS] Research Group 1978).

DME is characterized by swelling of the central part of the retina, or the macula, that is responsible for high-resolution vision. It is not uncommon for DME to co-exist with NPDR or PDR. When the area of swelling is located more than one disc diameter (approximately 1500 μm) away from the center of the fovea, the swelling constitutes a low threat to visual acuity (VA) and is regarded as nonclinically significant macular edema (Early Treatment Diabetic Retinopathy Study [ETDRS] Research Group 1985). When the DME involves the foveal center, vision is often compromised. Macular edema that involves the fovea or is at high risk of doing so is referred as clinically significant macular edema (CSME) (ETDRS Research Group, 1985). The mechanisms by which DME leads to vision loss remain largely unknown.

It has been fairly well established that DME arises from breakdown of the blood-retinal barrier, which leads to an abnormal accumulation of fluid and macromolecules within the layers of the retina. Early histologic findings include capillary basement membrane thickening, loss of pericytes, and loss of endothelial cells. Subsequent formation of microaneurysms, breakdown of the blood-retinal barrier, and consequent vascular leakage result in the pathogenesis of DME (Ho et al, 2012). The disruption of the blood-retinal barrier is thought to be largely due to compromise and increased permeability of the retinal vascular endothelium. The degree of retinal swelling is determined by Starling's law, which describes fluid movement as the outcome of the balance between hydrostatic and oncotic pressures in tissues and intravascular compartments.

DME may either occur in a focal area due to leakage from microaneurysms or in a diffuse fashion from breakdown of the blood-retinal barrier from the walls of a compromised capillary bed. The technique of focal laser photocoagulation, which was first described in the ETDRS protocol, results in closure of the leaking microaneurysms and cessation of the leakage. The ETDRS protocol also described a grid pattern of laser photocoagulation for treatment of diffuse leakage. The mechanism of action of this therapy remains unclear.

1.2 TREATMENT OF DIABETIC MACULAR EDEMA

The current standard of care of DME continues to change. Although focal laser photocoagulation plays a significant role in the management of patients with DME, its effect is often transient and inadequate. Fewer than 15% of patients gain more than three lines of best-corrected visual acuity at 3 years, whereas > 15% sustain moderate vision loss of more than three lines. Focal laser is less effective in cases of diffuse macular edema. Photocoagulation is a destructive therapy and can cause symptomatic paracentral scotomas, some of which can be disabling after multiple treatments. Vitrectomy is often reserved for the most refractory cases of DME and is associated with vitreous traction and bleeding. It also carries surgical risks (cataract formation, retinal detachment, and endophthalmitis) and has not been validated in large randomized studies. Many recent studies have shown promising visual results of intravitreal injections of inhibitors of vascular endothelial growth factor (VEGF). There is substantial evidence that suggests that these medications are superior to focal laser photocoagulation. However, many of these studies were designed to treat patients on a monthly basis. Because many of the patients with DME are young and because these injections are not a cure for the disease, the treatment burden can be substantial.

1.2.1 GLUCOSE CONTROL

Although glucose control does not have a direct effect on macular edema, it plays a role in the management of diabetic retinopathy as a primary and secondary prevention strategy. Improving blood glucose and blood pressure has been shown to slow the progression of retinopathy (DCCT Research Group, 1993; UKPDS Research Group, 1998a, 1998b). After 5 years of follow-up, there was a significant reduction in the risk of retinopathy progression by 76% in those being treated with intensive insulin therapy when compared to those with conventional insulin therapy. In the secondary intervention cohort, the progression of retinopathy was reduced by 54% in the intensive therapy group during the entire study period compared to those with conventional therapy. Additionally, the need for laser treatment was reduced by 56% in those in the intensive insulin therapy group. It should be noted that there was a higher frequency of "early worsening", or progression of retinopathy after a significant reduction in blood glucose levels, in the intensive therapy group. At 1 year, early worsening occurred in 13% of patients in the intensive therapy group compared to 8% in the conventional group. However, the large long-term risk reduction with intensive treatment was such that outcomes in the intensively treated subjects who had early worsening were similar to or more favorable than outcomes in the conventionally treated subjects who had not. With respect to macular edema, intensive therapy reduced the risk of onset of DME by 23% compared to conventional treatment.

1.2.2 LASER PHOTOCOAGULATION

Up until the last few years, laser photocoagulation remains the only therapy demonstrated to confer a clear-cut clinical benefit for any patients with DME (ETDRS Research Group 1985). Although laser photocoagulation does not restore vision on average, and relatively few patients gain clinically meaningful vision, it does slow the progression of moderate vision loss. In the ETDRS, subjects with DME assigned to early macular laser photocoagulation were half as likely to lose 15 or more letters on the ETDRS visual chart at 3 years than those who were not (12% vs. 25%). For those with CSME involving the foveal center, subjects assigned to receive early macular laser photocoagulation were also less likely to lose 15 or more letters at 3 years than those who were not (13% vs. 33%) (ETDRS Research Group 1987). In a more recent study comparing laser photocoagulation with intravitreal corticosteroids for DME involving the fovea, laser-treated patients gained a mean of + 1 ETDRS letter from baseline to 2 years, and + 5 ETDRS letters from baseline to 3 years. At 2 years, 14% of laser-treated patients had lost 15 or more ETDRS letters, and 18% had gained 15 or more ETDRS letters. Among patients who completed 3 years from study baseline, 30% of patients treated with laser photocoagulation improved by 15 or more ETDRS letters, and 9% lost 15 or more ETDRS letters (Diabetic Retinopathy Clinical Network,
2008 and 2009). Although photocoagulation for center involving CSME is a significant achievement in the management of diabetic retinopathy, laser treatment still leaves 9%−13% of patients losing more than 15 letters of vision

at the end of 3 years. Moreover, given that 69% of subjects with CSME in the ETDRS group had center involvement at presentation (ETDRS Research Group 1987), the unmet clinical need for better treatment of center involving CSME is significant.

1.2.3 INTRAVITREAL CORTICOSTEROIDS

Several non-randomized case series provided early evidence of the therapeutic effect from intravitreal corticosteroids for the management of DME. The biologic basis for the suggested beneficial effect most likely derives from the ability of corticosteroids to inhibit VEGF gene expression (Nauck et al, 1998). In a study of 26 eyes of 20 subjects by Jones an colleagues, a single 25 mg intravitreal injection of triamcinolone acetonide (TA; Kenalog®) was associated with a significant visual improvement ($P < 0.001$) from 20/165 at baseline to 20/105 at six months follow-up. In comparison, 16 subjects observed in a “control group” that received grid laser photocoagulation showed no improvement in vision. In a separate uncontrolled study of 16 eyes with CSME that did not respond to laser photocoagulation, a 4-mg intravitreal injection of TA resulted in mean VA improvement of 2.4, 2.4, and 1.3 Snellen lines and reduction of central macular thickness by 55%, 57%, and 38% measured at the 1, 3, and 6-month follow-up intervals, respectively (Martidis et al. 2002). In these and other studies with TA, the beneficial effects on retinal edema and vision were accompanied by elevated intraocular pressure (IOP) and cataract progression. Furthermore, optic nerve damage can occur if IOP remains persistently elevated.

To better understand the risk-benefit profile of steroids for DME, a larger study (693 subjects, 840 eyes) was undertaken by the Diabetic Retinopathy Clinical Research Network (2008, 2009) comparing repeat administration of two dosages
(1 mg or 4 mg) of intravitreal, preservative-free TA with focal/grid laser photocoagulation. Although mean visual acuity was better at 4 months in the 4 mg TA-treated group, by 1 year, no difference was observed in visual acuity among the treated groups, and at 2 and 3 years, mean VA improvement was better
in the laser-treated group. These results were not solely the result of increased rates of cataract formation in the TA groups. Thus, over follow-up periods of 2 and
3 years, focal/grid laser photocoagulation was both more effective and had fewer
side effects than TA in management of DME involving the fovea. Additionally, results from a separate randomized study conducted by the Diabetic Retinopathy Clinical Research Network comparing ranibizumab plus prompt or deferred focal laser, triamcinolone plus prompt laser, and prompt focal/grid laser alone showed that triamcinolone plus laser was no more effective than laser alone in improving BCVA through at least 1 year (DRCR.net, Ophthalmology 2010). In a subset of subjects who were pseudophakic, intravitreal triamcinolone

plus laser appeared more effective than laser alone, but was frequently associated with intraocular pressure elevation.

1.2.4 VITRECTOMY

In a subset of patients with DME, vitreous traction leads to a mechanical distortion of retinal anatomy. These mechanical vector forces on the retina may cause and exacerbate macular edema. Cases such as these, in which mechanical traction complicates the pathology of macular edema, are less responsive to laser therapy and presumably intravitreal corticosteroids Vitrectomy may play a role in this setting to prevent severe vision loss Some studies of subjects with DME have reported DME resolution in 45-82% of eyes, and visual improvement by two or more lines in 49-86% if subjects (van Effenterre et al, 1993; Tachi and Ogino, 1996; Pendergast et al, 2000).

1.2.5. PEGAPTANIB SODIUM INJECTION

Results from an experimental anti-VEGF therapy, pegaptanib sodium injection (Macugen®), showed a biologic effect in DME. Pegaptanib is an inhibitory aptamer, currently approved for the treatment of neovascular (wet) age-related macular degeneration (AMD). It is typically delivered as an intravitreal injection every 6 weeks. Positive results from a phase 3, multicenter, randomized study (n = 260) of intravitreal pegaptanib compared with sham injection for DME have been published (Sultan et al, 2011). This clinical trial compared 0.3 mg of intravitreal pegaptanib every 6 weeks with a sham injection. Patients could receive macular photocoagulation in the study after week 18 based on ETDRS criteria. No safety issues were identified in this study and pegaptanib was superior to sham injection with respect to 2-line visual acuity gains at month 12. 37% of those treated with pegaptanib demonstrated a 2-line visual benefit compared to 20% in the sham injection group ($p = 0.0047$). Mean BCVA at month 12 was +5.1 letters (pegaptanib) compared with +1.2 letters (sham; $p < 0.05$).

1.2.6 BEVACIZUMAB

Bevacizumab (marketed under the trade name Avastin®) is an anti-VEGF monoclonal antibody with similar mechanism of action to ranibizumab. Avastin is approved for the systemic treatment of colorectal cancer in combination with 5-fluorouracil-based chemotherapy, and for the first-line treatment of metastatic non-squamous, non-small cell lung cancer in combination with carboplatin and paclitaxel. The significant unmet need for better therapies in DME has caused a surge in investigations (primarily case reports and case series) of off-label intravitreal use of bevacizumab as salvage and primary therapy in DME.

While many of the studies are small and uncontrolled, they suggest evidence of biologic activity through effect on macular anatomy and visual function. Most

recently, the level II Bevacizumab or Laser Therapy (BOLT) study reported 2-year results comparing intravitreal bevacizumab 1.25 mg versus focal macular laser treatment for DME in 80 subjects (Rajendram et al, 2012 epub ahead of print). Median gain in BCVA was superior for intravitreal bevacizumab (+9 letters) compared with macular laser treatment (+2.5 letters; p = 0.005). Mean central macular thickness reduction was slightly greater, but not statistically significant, in the intravitreal bevacizumab group at 24 months (-146 μm) versus the macular laser treatment group (-118 μm; p = 0.62).

1.2.7 AFLIBERCEPT

Aflibercept (Eylea®), also known as VEGF Trap-Eye (VTE), has been approved for treatment of DME. It is currently approved for treatment of neovascular AMD and for macular edema secondary to central retinal vein occlusions as well. The phase II DA VINCI trial demonstrated the efficacy of VTE compared with macular laser for the treatment of DME. In this level II study, 221 patients with CSME involving the central macula were randomized to 1 of 5 treatment protocols. At 24 weeks, treatment groups with VTE showed visual acuity benefits between +8.5 and +11.4 letters compared to +2.5 letters in the laser group ($p < 0.0085$). Adverse events reported were consistent with other intravitreal treatment agents.

1.3 RANIBIZUMAB AND DIABETIC MACULAR EDEMA

The rationale for VEGF inhibition in DME is well established. DME is characterized by a local breakdown of the blood-retinal barrier, resulting in vascular leakage through changes in tight junctions, upregulation of intra-endothelial vesicles, and permeation of retinal vascular endothelial and retinal pigment epithelial cells that have undergone degenerative changes (Vinores et al, 1999). It is well established that vascular leakage in patients with diabetic retinopathy is promoted by VEGF (Witmer et al, 2003). Intraocular expression and levels of VEGF are markedly increased and correlate with the severity and degree of retinopathy (Funatsu et al, 2003, 2005, 2006). VEGF, which is upregulated by interluekin-6 (another key diffusible factor in DME), exerts direct biologic effect on endothelial cells through intercellular adhesion molecule-1, with downstream effects on intraretinal leukostasis, monocyte chemotaxis, tight-junction changes, and subsequent blood-retinal barrier breakdown (Cohen et al, 1996; Ishida et al, 2003).

Unmet need drives demand for new alternative therapies for DME. There is growing clinical rationale for VEGF inhibition by ranibizumab in the treatment of DME. Limited clinical experience with ranibizumab in DME was first available in small, uncontrolled investigator-sponsored trials (ISTs), for which Genentech has provided support. In a series of 10 subjects studied in a Phase I IST supported by Genentech, Chun et al (2006) showed that three monthly injections of 0.3 mg or 0.5 mg ranibizumab were tolerated by subjects with center-involved CSME. At 3 months, 4 of 10 subjects gained ≥ 15 letters, 5 of

10 subjects gained ≥ 10 letters, and 8 of 10 subjects gained ≥ 1 letter. At month 3, the 0.5 mg and 0.3 mg ranibizumab groups demonstrated an improvement of vision by +7.8 letters and +12 letters, respectively. Although subjects in both dose arms showed improvement in BCVA from baseline, the anatomic and functional outcomes were better for the high-dose group.

Multiple level I studies (DRCR, RESTORE, RISE, RIDE) have demonstrated the efficacy of intravitreal ranbizumab for the treatment of DME. Level I data from the DRCR Network showed that patients treated with 0.5 mg ranibizumab plus prompt laser (n = 187) or deferred laser (≥ 24 weeks; n = 188) had significantly better visual acuity outcomes at the 1 year mark than those treated with sham injection plus prompt laser (n = 293). Mean change in BCVA in the ranibizumab groups were +9 letters compared to +3 for the sham injection group. The 2-year results demonstrated similar findings.

The RESTORE trial, as well as the RISE and RIDE trials, supported the indication for ranibizumab for the treatment of DME. All three of these studies showed significant visual gains in the ranibizumab treated groups compared to those not treated with ranibizumab.

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 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 recipients 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 $\geq$ 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 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 $\geq$ 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 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 Cohort1.

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

2. OBJECTIVES

This trial will assess the safety, tolerability and efficacy of a treat and extend management protocol for DME. Patients will be enrolled into one of three treatment groups: (1) monthly intravitreal injections of 0.3 mg ranibizumab (Monthly Cohort, 30 eyes); (2) monthly intravitreal injections of 0.3 mg ranibizumab for 4 visits, followed by a "TReat and EXtend" protocol based on pre-specified criteria of disease activity (T-REX cohort, 60 eyes); (3) monthly intravitreal injections of 0.3 mg ranibizumab for 4 visits combined with adjunctive GuIded focal LAser macular photocoaulation to microaneurysms at week 4 and then every 3 months if leakage is present on fluorescein angiography, followed by a treat and extend protocol based on pre-specified criteria of disease activity (GILA cohort, 60 eyes).

2.1 Primary Objective

- Mean change in ETDRS visual acuity at 24 months (week 92 – week 107) from Day 0.

2.2 Secondary Objectives

- Incidence and severity of adverse events (ocular and non-ocular).
- Total number of intravitreal injections required during each year of the study period (week 52, week 104, and week 156). In a separate proof of concept analysis, the number of intravitreal injections in the TREX and GILA cohorts over the 36-month study period will be compared with that of the other two cohorts ($p = 0.20$).
- Total number of office visits and imaging studies performed during each year of the study period.
- Mean change in central foveal thickness per SD-OCT from randomization to 12 months (week46 – week 57),randomization to 24 months (week 92 – week 107) , and randomization to 36 months (week 156).
- Percentage of eyes gaining or losing 3 lines of vision or more and 1 line of vision or more at 6 months (week 22 – week 29),12 months (week 46 – week

57),18 months (week 70 – week 85),24 months (week 92 – week 107), and 36 months (week 156) from Day 0.

- Noninferiority comparison (margin of 9 letters) of mean change in ETDRS vision from Day 0 to 24 months (week 92 – week 107) between the three study groups.

- The percentage of eyes which show progression of proliferative diabetic retinopathy requiring panretinal photocoagulation and/or pars plana vitrectomy over the 36-month study period.

- The percentage of eyes in the TREX and GILA cohorts who are eligible to begin the extension phase after 4 treatment visits.

- For TREX and GILA Cohorts, the time to achieve a "Secondary or Tertiary Baseline" retinal thickness.
- Percentage of eyes in each cohort that have shown a two-step change (increase and decrease) in diabetic retinopathy at 24 months and 36 months from day 0.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open-label, phase I/II trial, which will assess the safety, tolerability and efficacy of a treat and extend management protocol for DME. Eyes which meet screening criteria will be enrolled into one of three treatment groups: (1) monthly intravitreal injections of 0.3 mg ranibizumab (Monthly Cohort, 30 eyes); (2) monthly intravitreal injections of 0.3 mg ranibizumab for 4 visits, followed by a "TReat and EXtend" protocol based on pre-specified criteria of disease activity (T-REX cohort, 60 eyes); (3) monthly intravitreal injections of 0.3 mg ranibizumab for 4 visits combined with adjunctive GuIded focal LAser photocoaulation to microaneurysms at week 4 and then every 3 months if leakage is present on fluorescein angiography, followed by a treat and extend protocol based on pre-specified criteria of disease activity (GILA cohort, 60 eyes).

Randomization Scheme:

All eyes which satisfy all inclusion/exclusion criteria will be randomized 1:2:2 into the Monthly:TREX:GILA Cohorts.

3 Treatment arms:

1. **Monthly Cohort (30 eyes)**: Monthly intravitreal injections of 0.3 mg ranibizumab for 36 months, unless they meet pre-specified criteria for PRN treatment (indicated below). Treatment will begin at Day 0 and

subsequent study visits should be scheduled to occur every 28 (±7) days relative to the date of the first injection. Dosing should not occur earlier than 21 days after previous treatments.

Starting at week 104, study eyes will have the opportunity to undergo treatment on a pro re nata (PRN) basis. Thus, eyes who have a central subfield thickness (CST) ≤ 325 microns at the week 104 visit, will not be given treatment at week 104. Eyes will continue to be seen every 4 weeks and will be given an intravitreal injection of ranibizumab 0.3 mg only if the CST is > 325 microns. Eyes will also receive treatment if there is a > 5 letter loss due to DME (compared to the vision at week 104), regardless of thickness on OCT.

Subjects will be evaluated for focal laser treatment at week 116, week 128, week 140, and week 152. If the subject has received ≥ 2 intravitreal injections of ranibizumab within the prior 90 day period, then fluorescein angiography will be performed and focal laser treatment will be applied to any leaking microaneurysms. If the patient does not meet this criteria for focal laser treatment, then fluorescein angiography and focal laser treatment will be deferred and reassessed at the subsequent laser evaluation visit. Focal laser treatment and focal laser re-treatment will be administered no more than once every 90 days.

Focal laser therapy will be applied to all leaking microaneurysms on fluorescein angiography. Focal laser therapy will not be applied if significant macular ischemia is present involving the foveal avascular zone (once this has been determined additional fluorescein angiography and focal laser treatment planning should not be performed as the subject will no longer be eligible for focal laser treatment). Focal laser will also not be applied if treatment is considered too close to the foveal avascular zone or to macular edema not related to DME (cystoid macular edema, etc.). If no microaneurysms are present on fluorescein angiography, then focal laser therapy should be deferred and reassessed with repeat fluorescein angiography at the first visit that occurs after 90 days.

2. **TREX Cohort (60 eyes)**: Monthly intravitreal injections of 0.3 mg ranibizumab for four (4) visits. If the central foveal thickness is ≤ 325 μm at the fourth visit (Week 12) then the baseline retinal thickness will be recorded, the eye will receive 0.3 mg ranibizumab and the study eye will begin the extension phase of the study. For all subsequent visits in the extension phase, appropriate changes to the treatment interval with 0.3 mg ranibizumab (i.e. extend, maintain, reduce) will be made based on pre-specified SD-OCT criteria (SEE TREATMENT INTERVAL DETERMINATION). Treatment is rendered at

every visit, no earlier than 7 days before the target date and no later than 7 days after the target date, but the time between visits is individualized based on each subject's response to treatment. Dosing should not occur earlier than 21 days after previous treatments.

If the central foveal thickness is > 325 μm at week 12, the patient will continue to receive monthly intravitreal injections of 0.3 mg ranbizumab until the central foveal thickness is ≤ 325 μm. Once the central foveal thickness is ≤ 325 μm, the study eye will begin the extension phase of the study.

Starting at week 104, study eyes will have the opportunity to undergo treatment on a pro re nata (PRN) basis. Thus, eyes who have a central subfield thickness (CST) ≤ 325 microns at the week 104 visit, will not be given treatment at week 104. Starting at week 104, eyes will be seen every 4 weeks and will be given an intravitreal injection of ranibizumab 0.3 mg only if the CST is > 325 microns. Eyes will also receive treatment if there is a > 5 letter loss due to DME (compared to the vision at week 104), regardless of thickness on OCT.

Subjects will be evaluated for focal laser treatment at week 116, week 128, week 140, and week 152. If the subject has received ≥ 2 intravitreal injections of ranibizumab within the prior 90 day period, then fluorescein angiography will be performed and focal laser treatment will be applied to any leaking microaneurysms. If the patient does not meet this criteria for focal laser treatment, then fluorescein angiography and focal laser treatment will be deferred and reassessed at the subsequent laser evaluation visit. Focal laser treatment and focal laser re-treatment will be administered no more than once every 90 days.

Focal laser therapy will be applied to all leaking microaneurysms on fluorescein angiography. Focal laser therapy will not be applied if significant macular ischemia is present involving the foveal avascular zone (once this has been determined additional fluorescein angiography and focal laser treatment planning should not be performed as the subject will no longer be eligible for focal laser treatment). Focal laser will also not be applied if treatment is considered too close to the foveal avascular zone or to macular edema not related to DME (cystoid macular edema, etc.). If no microaneurysms are present on fluorescein angiography, then focal laser therapy should be deferred and reassessed with repeat fluorescein angiography at the first visit that occurs after 90 days.

3. **GILA Cohort (60 eyes):** Monthly intravitreal injections of 0.3 mg ranibizumab for four visits combined with GuIded LAser (GILA) photocoagulation to all microaneurysms in the area of DME at the second visit (Week 4). Fluorescein angiography is to be repeated approximately every 3 months (the first visit that occurs ≥ 90 days from the preceeding fluorescein angiography visit). Guided laser will be repeated at those visits if leakage is present from microaneurysms.

If the central foveal thickness is ≤ 325 μm at Week 12 then the baseline retinal thickness will be recorded, the eye will receive 0.3 mg ranibizumab, and the study eye will begin the extension phase of the study. In the extension phase, appropriate changes to the treatment interval with 0.3 mg ranibizumab (i.e. extend, maintain, reduce) will be made based on pre-specified SD-OCT criteria (SEE TREATMENT INTERVAL DETERMINATION). Treatment is rendered at every visit, no earlier than 7 days before the target date and no later than 7 days after the target date, but the time between visits is individualized based on each subject's response to treatment. Dosing should not occur earlier than 21 days after previous treatments.

If the central foveal thickness is > 325 μm at week 12, then the patient will continue to receive monthly intravitreal injections of 0.3 mg ranbizumab and possible guided laser photocoagulation, approximately every 3 months until the central foveal thickness is ≤ 325 μm. Once the central foveal thickness is ≤ 325 μm, then the study eye will begin the extension phase of the study.

Starting at week 104, study eyes will have the opportunity to undergo treatment on a pro re nata (PRN) basis. Thus, eyes who have a central subfield thickness (CST) ≤ 325 microns at the week 104 visit, will not be given treatment at week 104. Starting at week 104, eyes will be seen every 4 weeks and will be given an intravitreal injection of ranibizumab 0.3 mg only if the CST is > 325 microns. Eyes will also receive treatment if there is a > 5 letter loss due to DME (compared to the vision at week 104), regardless of thickness on OCT.

After week 104, subjects will be evaluated for focal laser treatment in the same manner as the Monthly and TREX Cohorts. Subjects will be evaluated for focal laser treatment at week 116, week 128, week 140, and week 152. If the subject has received ≥ 2 intravitreal injections of ranibizumab within the prior 90 day period, then fluorescein angiography will be performed and focal laser treatment will be applied to any leaking microaneurysms. If the patient does not meet this criteria for focal laser treatment, then fluorescein angiography and focal laser treatment will be deferred and reassessed at the subsequent laser evaluation visit. Focal

laser treatment and focal laser re-treatment will be administered no more than once every 90 days.

Focal laser therapy will be applied to all leaking microaneurysms on fluorescein angiography. Focal laser therapy will not be applied if significant macular ischemia is present involving the foveal avascular zone (once this has been determined additional fluorescein angiography and focal laser treatment planning should not be performed as the subject will no longer be eligible for focal laser treatment). Focal laser will also not be applied if treatment is considered too close to the foveal avascular zone or to macular edema not related to DME (cystoid macular edema, etc.). If no microaneurysms are present on fluorescein angiography, then focal laser therapy should be deferred and reassessed with repeat fluorescein angiography at the first visit that occurs after 90 days.

Baseline Retinal Thickness Measurement for the TREX and GILA Cohorts:

For eyes which have a central foveal thickness $\leq$ 325 μm at week 12, a "Primary Baseline" retinal thickness will be defined as the thinnest central foveal thickness on SD-OCT over the first four visits of monthly treatment. Eyes which have a central foveal thickness > 325 μm at week 12 will continue to receive monthly intravitreal injections of 0.3 mg ranibizumab until the central foveal thickness is $\leq$ 325 μm, at which point their "Primary Baseline" retinal thickness will be established. Eyes in the GILA cohort will continue to receive guided laser photocoagulation to microaneurysms every 3 months if leakage is present on fluorescein angiography.

If at any point in the study period, the study eye has improved more than 20% from the primary baseline thickness for three consecutive visits and there is less than 50 microns of variability in central foveal thickness between these visits, then a "Secondary Baseline" retinal thickness will be established. This "Secondary Baseline" retinal thickness will then be used for treatment interval determinations from that point forward. If the study eye has improved more than 20% from the secondary baseline thickness for three consecutive visits and there is less than 50 microns of variability in central foveal thickness between these visits, then a "Tertiary Baseline" retinal thickness will be established. This "Tertiary Baseline" retinal thickness will then be used for treatment interval determinations from that point forward.

Treatment Interval Determination For TREX and GILA Cohorts:

Starting at Week 12, if the central foveal thickness is ≤ 325 μm, then the following re-treatment criteria will be applied at all visits. Eyes with central foveal thickness > 325 μm at week 12 will continue to receive monthly injections of 0.3 mg ranibizumab until the central foveal thickness is ≤ 325 μm, at which time the following re-treatment criteria will be applied at all visits. Eyes in the GILA cohort will continue to receive guided laser photocoagulation to microaneurysms every 3 months if leakage is present on fluorescein angiography. This treatment interval determination will continue up to week 104.

Extend Interval (by 2 weeks):
1. If the central foveal thickness on SD-OCT is within ≤10% thicker or thinner compared to baseline (primary, secondary, or tertiary baseline) retinal thickness.

Maintain Interval:
1. If the central foveal thickness is between >10% thicker and ≤ 20% thicker from the baseline retinal thickness (primary, secondary or tertiary baseline) OR
2. If the central foveal thickness is > 10% thinner from baseline retinal thickness (primary, secondary or tertiary baseline).

Reduce Interval (by 2 weeks):
1. If the central foveal thickness is > 20% thicker from baseline retinal thickness (primary, secondary or tertiary baseline).

Reduce Interval to 4 weeks:
1. If there is a loss of more than 15 letters from best previous ETDRS vision, due to DME.

Study eyes which have not met criteria allowing them to extend to greater then or equal to 6 weeks for two consecutive visits by the week 52 (hard endpoint) visit will receive a series of three intravitreal injections of ranibizumab 0.3 mg every 4 weeks regardless of SD-OCT measurement. This series of three injections every 4 weeks will begin at the first treatment visit that occurs after the 52 week hard endpoint visit.The study eye will resume treatment interval determinations based on the pre-specified criteria at the time of the third monthly intravitreal injection.

The interval between study injections will not exceed 12 weeks in year one of the study. The interval between study injections can be extended to, but not more than, 16 weeks in year two of the study.

Enrolled subjects will have ETDRS BCVA, complete ophthalmic examination and SD-OCT evaluation using Spectralis machines at each visit. Fluorescein angiography will be done in the Monthly and TREX Cohorts at baseline (screening visit) and again at week 12, week 52, and week 104 or visits closest

to. Fluorescein angiography will be done in the GILA Cohort at baseline (screening visit), week 4, and every 90 days or greater (first visit that occurs ≥ 90 days from previous fluorescein angiogram). See Appendix A for schedule of events from screening visit to week 104 and Appendix A.1 for the schedule of events between week 108 and week 156.

End-Point Visits
Subjects will continue to receive study treatments according to the above treatment protocol until week 155. A "Hard End-Point Visit" will occur at week 52,week 104, and week 156. A "Biologic End-Point Visit" will occur 4 weeks after the previous injection near the 12-month time point (week 46 – week 57),24-month time point (week 92 – week 107). Only best corrected visual acuity and SD-OCT measurements will be recorded at these endpoint visits. No study treatment will be given at these end-point visits, unless the patient has a regular study treatment visit that occurs at these time points.

Fellow eyes not enrolled into a study group that have DME during the course of the study may be treated with standard of care macular laser photocoagulation and/or intravitreal injections of 0.3 mg of ranibizumab at the investigator's discretion. Ranibizumab will be provided by Genentech for treatment of DME in the fellow eye.

3.2 Rationale For Study Design

Diabetic macular edema (DME) is the most common cause of severe vision loss in Americans under 60. However, even mild to moderate vision loss from DME is impactful, since it strikes individuals often in the productive periods of their lives. Until now, interventions for diabetic retinopathy have been focused on maintaining current visual function or slowing the rate of vision loss.

The RISE and RIDE studies were parallel, phase III, double-masked clinical trials designed to evaluate the efficacy and safety of ranibizumab in the treatment of DME. In similarly designed protocols, patients were treated with monthly injections of ranibizumab (0.3 mg and 0.5 mg) versus sham monthly injections (all arms could receive macular laser photocoagulation from month 3 if meeting predefined criteria). The 2-year results demonstrated a statistically significant benefit from ranibizumab across numerous parameters, including mean change in visual acuity, percent of 10 letter and 15 letter gainers, and reduction in retinal thickness by OCT. Other smaller clinical trials have also demonstrated superiority of ranibizumab to laser alone.

Rationale for "Treat and Extend" versus fixed dosing
RISE and RIDE employed fixed dosing strategies during the entire 3-year mandatory treatment period. Like age-related macular degeneration, the best data available suggests that no alternative to monthly dosing has been

identified. However, monthly dosing of ranibizumab is problematic in DME for several reasons. First, compliance is often difficult in this population. In the RISE and RIDE studies, and multiple DRCR.net protocols, dropout rates consistently approach 10% per year. In addition, the natural history of DME suggests that long-term treatment will be required. This is quite different from age-related macular degeneration and retinal vein occlusion, where the disease activity wanes over time in many patients.

Because of these and other realities, alternatives to chronic, monthly dosing need to be explored. The DRCR Network has employed a "4-2-7" strategy in which patients receive 4 mandatory doses, followed by PRN dosing based on clinical response. In this proposal, an initial loading dose of 4 injections is proposed because much of the vision gains in RISE and RIDE were attained during the first 120 days. By only extending the interval by 2 weeks at each successful visit, it is postulated that the gains achieved early on may be maintained without aggressive recurrence. Once a patient reaches an interval that limits the control of disease activity, their recurrence is likely to be mild or even subclinical. At one year, it is likely that there will be a wide variety of dosing intervals in the cohort, based on disease activity, addition of panretinal photocoagulation, or other factors. What is unknown is how the visual outcomes with a "treat and extend" protocol will compare to the RISE and RIDE trials.

<u>Rationale for GuIded LAser photocoagulation</u>
Since the publication of the Early Treatment Diabetic Retinopathy Study (ETDRS), macular laser photocoagulation has been vital in the management of DME. Because of the retina community's positive experience with macular laser, it is likely that many clinicians will utilize some form of combination therapy in clinical practice. Recent data published by the Diabetic Retinopathy Clinical Research Network's (DRCR.net) protocol I offers some direction for inclusion of laser in this protocol. Although faithful treatment with ranibizumab alone offered the best final visual outcome, the number of injections required at long-term follow-up were less in patients that received macular laser sometime during their treatment. In Protocol I, patients who received deferred laser had better visual outcomes compared to those receiving laser at entry. It is felt that by treating initially with ranbizumab caused some resolution of the macular edema, which allowed for better treatment effect with lower laser power settings, thereby minimizing laser-induced scotomas.

A potential drawback of the modified-ETDRS focal laser protocol employed in most DME trials is that the laser application is guided manually, which can be difficult in a living, moving patient. Accuracy of treatment delivery is always a concern and collateral damage to the neurosensory retina can lead to vision loss in some patients. The navigated laser (NAVILAS) photocoagulator is a novel laser delivery system that utilizes a retinal eye-tracking and laser stabilization system (Kozak et al, 2012). It was designed to improve accuracy

and to provide the ability to localize microaneurysms, which may be difficult to target using a traditional slit-lamp laser. Several studies have shown that the NAVILAS system is safe and achieves a higher rate of accuracy in photocoagulation treatments than standard manual-technique methods (Kozak et al, 2012). Because the NAVILAS photocoagulator uses a camera-based system, larger areas of the retina can be visualized, there is less glare artifact, and the patient is more comfortable (Kernt et al, 2011). A further advantage of the NAVILAS system is that it allows standardized laser treatment to all microanuerysms in the area of DME, which would be beneficial for this study and future clinical trial designs.

Summary

To date, evidence from multiple clinical trials suggests that monthly ranibizumab combined with laser sometime during the beginning of therapy offers the best long-term clinical outcomes. Although a promising therapy, there are limitations to chronic monthly therapy. By exploring a treat and extend strategy once disease activity is under control, the investigators postulate that extending maintenance intervals can preserve the gains of initial monthly injections and reduce treatment burden.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measure

- Mean change in ETDRS visual acuity at 24 months (week 92 – week 107) from Day 0.

3.3.2 Secondary Outcome Measures

- Incidence and severity of adverse events (ocular and non-ocular).
- Total number of intravitreal injections required during each year of the study period (week 52, week 104, and week 156). In a separate proof of concept analysis, the number of intravitreal injections in the TREX and GILA cohorts over the 36-month study period will be compared with that of the other two cohorts ($p = 0.20$)
- Total number of office visits and imaging studies performed during each year of the study period (week 52, week 104, and week 156).
- Mean change in central foveal thickness per SDOCT from randomization to 12 months (week 46 – week 57),randomization to 24 months (week 92 – week 107), and randomization to 36 months (week 156).
- Percentage of eyes gaining or losing 3 lines of vision or more and 1 line of vision or more at 6 months (week 22 – week 29),12 months (week 46 – week 57), 18

months (week 70 – week 85),24 months (week 92 – week 107), and 36 months (week 156) from Day 0.

- Noninferiority comparison (margin of 9 letters) of mean change in ETDRS vision from Day 0 to 24 months (week 92 – week 107) between the three study groups.

- The percentage of eyes which show progression of proliferative diabetic retinopathy requiring panretinal photocoagulation and/or pars plana vitrectomy over the 36-month study period.

- The percentage of eyes in the TREX and GILA cohorts who are eligible to begin the extension phase after 4 treatment visits.
- For TREX and GILA Cohorts, the time to achieve a “Secondary or Tertiary Baseline” retinal thickness.
- Percentage of eyes in each cohort that have shown a two-step change (increase and decrease) in diabetic retinopathy at 24 months and 36 months from day 0.

3.4 SAFETY PLAN

The safety assessments to be conducted for this study are listed in Section 5 and Appendix A.

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

To minimize the risks of intraocular injections, all injections will be performed employing surgical sterile techniques as described in Appendix B. Following each injection, subjects will have a retinal examination either by indirect ophthalmoscopy or checking subject’s ability to see (at investigator’s discretion) to ensure that there is a good perfusion of retinal vessels.

Study drug administration will be held for subjects who experience certain ocular events or infection events. In the event any subject develops an adverse event in the study eye that is considered by the physician to be severe in

intensity, serious consideration should be given to withdrawing the subject from the study.

All adverse events will be reviewed by the PI on an ongoing basis.

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

150 eyes from approximately 3 sites in the United States will be enrolled. Eligible subjects who have provided informed consent will be screened for eligibility before the initiation of any study procedures. Screening evaluations may be performed at any time within the 14 days preceding Day 0. These subjects must have center involved diabetic macular edema, with evidence of activity seen on SD-OCT.

(See attached 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 of age

- Patient-related considerations
- For sexually active women of childbearing potential, agreement to the use of an appropriate form of contraception (or abstinence) for the duration of the study
- Although no birth control method is 100% effective, the following are considered effective means of contraception: surgical sterilization, use of oral contraceptives, barrier contraception using either a condom or diaphragm with spermicidal gel, an intrauterine device, or contraceptive hormone implant or patch. A patient's primary care physician, obstetrician, or gynecologist should be consulted regarding an appropriate form of birth control.

- Ability and willingness to return for all scheduled visits and assessments

Disease-related considerations

- The presence of center-involving diabetic macular edema on clinical exam and SD-OCT
- Best corrected visual acuity in the study eye, using ETDRS testing, between 20/25 and 20/320 (Snellen equivalent), inclusive.
- Clear ocular media and adequate pupillary dilation to permit good quality fundus imaging.

4.1.3 Exclusion Criteria

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

General Exclusion Criteria

- Pregnancy (positive urine 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

Ocular Exclusion Criteria

Prior Ocular Treatment

- History of active proliferative diabetic retinopathy in the study eye on clinical exam
- History of vitrectomy surgery, submacular surgery, or other intraocular surgical intervention for diabetic macular edema in the study eye
- Any previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection, anti-VEGF drugs including ranibizumab, or device implantation) in the study eye within 90 days of the screening visit.
- History of prior laser macular photocoagulation more than 90 days prior to screening will be eligible for study inclusion. However, if the investigator does not feel that additional laser photocoagulation can be safely performed or would benefit the patient, then the eye in consideration will be excluded.

- Evidence of vitreomacular interface abnormality or epiretinal membranes which may be responsible for macular edema

Concurrent Ocular Conditions

- Any concurrent intraocular condition in the study eye (e.g., cataract or macular degeneration) that, in the opinion of the investigator, could either:

  Require medical or surgical intervention during the 24-month study period to prevent or treat visual loss that might result from that condition; or if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of BCVA over the 24-month study period.

- Active intraocular inflammation (grade trace or above) in the study eye
- Current vitreous hemorrhage in the study eye
- History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Aphakia in the study eye
- Intraocular surgery (including cataract surgery) in the study eye within 3 months preceding Day 0
- Uncontrolled glaucoma in the study eye (defined as IOP ≥ 30 mmHg despite treatment with anti-glaucoma medication)
- History of glaucoma-filtering surgery in the study eye
- History of corneal transplant in the study eye
- History of pars plana vitrectomy

Concurrent Systemic Conditions

- Any history of use of systemic anti-VEGF agents
- Uncontrolled blood pressure (defined as systolic > 180 mmHg and/or diastolic > 110 mmHg while patient is sitting)

  If a patient's initial reading exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure needs to be controlled by antihypertensive medication, the patient can become eligible if medication is taken continuously for at least 30 days prior to Day 0.
- Atrial fibrillation not managed by patient's primary care physician or cardiologist within 3 months of screening visit
- Women of childbearing potential not using adequate contraception (as defined in the inclusion criteria).

  A woman is considered not to be of childbearing potential if she is postmenopausal, defined by amenorrhea for at

least 1 year in a woman > 45 years old; or has undergone hysterectomy and/or bilateral oophorectomy.

- History of stroke within the last 3 months of screening visit
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications
- Current treatment for active systemic infection
- Active malignancy
- History of allergy to fluorescein, not amenable to treatment
- Inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analyzed and graded by the reading center
- Inability to comply with study or follow-up procedures
- Previous participation in any studies of investigational drugs within 1 month preceding Day 0 (excluding vitamins and minerals)

4.2 METHOD OF TREATMENT ASSIGNMENT

All eyes which satisfy all inclusion/exclusion criteria will be randomized 1:2:2 into the Monthly:TREX:GILA Cohorts. Screening evaluations may be performed at any time within the 14 days preceding Day 0. Randomization will occur at Day 0.

Baseline Measurement For the TREX and GILA cohorts:

Eyes which have a central foveal thickness $\leq$ 325 μm at week 12, a "Primary Baseline" retinal thickness will be defined as the thinnest central foveal thickness on SD-OCT over the first four visits of monthly treatment. Eyes which have a central foveal thickness > 325 μm at week 12 will continue to receive monthly intravitreal injections of 0.3 mg ranibizumab and guided laser photocoagulation every 3 months if leakage is present on fluorescein angiography until the central foveal thickness is $\leq$ 325 μm, at which point their "Primary Baseline" retinal thickness will be established.

If at any point in the study period, the study eye has improved more than 20% from the primary baseline thickness for three consecutive visits and there is less than 50 microns of variability in central foveal thickness between these visits, then a "Secondary Baseline" retinal thickness will be established. This "Secondary Baseline" retinal thickness will then be used for treatment interval determinations from that point forward. If the study eye has improved more than 20% from the secondary baseline thickness for three consecutive visits and there

is less than 50 microns of variability in central foveal thickness between these visits, then a “Tertiary Baseline” retinal thickness will be established. This “Tertiary Baseline” retinal thickness will then be used for treatment interval determinations from that point forward.

Treatment Groups:

Monthly Cohort (30 eyes) – Study eyes will receive intravitreal injections of 0.3 mg ranibizumab every 28 days (+/- 7) for 36 months, relative to the date of the first injection (Day 0), unless indicated below.

Starting at week 104, study eyes will have the opportunity to undergo treatment on a pro re nata (PRN) basis. Thus, eyes who have a central subfield thickness (CST) ≤ 325 microns at the week 104 visit, will not be given treatment at week 104. Eyes will continue to be seen every 4 weeks and will be given an intravitreal injection of ranibizumab 0.3 mg only if the CST is > 325 microns. Eyes will also receive treatment if there is a > 5 letter loss due to DME (compared to the vision at week 104), regardless of thickness on OCT.

Subjects will be evaluated for focal laser treatment at week 116, week 128, week 140, and week 152. If the subject has received ≥ 2 intravitreal injections of ranibizumab within the prior 90 day period, then fluorescein angiography will be performed and focal laser treatment will be applied to any leaking microaneurysms. If the patient does not meet this criteria for focal laser treatment, then fluorescein angiography and focal laser treatment will be deferred and reassessed at the subsequent laser evaluation visit. Focal laser treatment and focal laser re-treatment will be administered no more than once every 90 days.

Focal laser therapy will be applied to all leaking microaneurysms on fluorescein angiography. Focal laser therapy will not be applied if significant macular ischemia is present involving the foveal avascular zone (once this has been determined additional fluorescein angiography and focal laser treatment planning should not be performed as the subject will no longer be eligible for focal laser treatment). Focal laser will also not be applied if treatment is considered too close to the foveal avascular zone or to macular edema not related to DME (cystoid macular edema, etc.). If no microaneurysms are present on fluorescein angiography, then focal laser therapy should be deferred and reassessed with repeat fluorescein angiography at the first visit that occurs after 90 days.

TREX Cohort (60 eyes) – Monthly intravitreal injections of 0.3 mg ranibizumab for four visits. At the fourth visit (Week 12), if the central foveal thickness is $\leq$ 325 μm then the eye will receive 0.3 mg ranibizumab and begin the extension phase of the study. For all subsequent visits in the extension phase, appropriate changes to the treatment interval with 0.3 mg ranibizumab (i.e. extend, maintain, reduce) will be made based on pre-specified SD-OCT criteria. Treatment is rendered at every visit, no earlier than 7 days before the target date and no later than 7 days after the target date, but the time between visits is individualized based on each subject's response to treatment. If the central foveal thickness is > 325 μm at week 12, then the patient will continue to receive monthly intravitreal injections of 0.3 mg ranbizumab until the central foveal thickness is $\leq$ 325 μm. Once the central foveal thickness is $\leq$ 325 μm, then the study eye will begin the extension phase of the study.

Starting at week 104, study eyes will have the opportunity to undergo treatment on a pro re nata (PRN) basis. Thus, eyes who have a central subfield thickness (CST) ≤ 325 microns at the week 104 visit, will not be given treatment at week 104. Starting at week 104, eyes will be seen every 4 weeks and will be given an intravitreal injection of ranibizumab 0.3 mg only if the CST is > 325 microns. Eyes will also receive treatment if there is a > 5 letter loss due to DME (compared to the vision at week 104), regardless of thickness on OCT.

Subjects will be evaluated for focal laser treatment at week 116, week 128, week 140, and week 152. If the subject has received $\geq$ 2 intravitreal injections of ranibizumab within the prior 90 day period, then fluorescein angiography will be performed and focal laser treatment will be applied to any leaking microaneurysms. If the patient does not meet this criteria for focal laser treatment, then fluorescein angiography and focal laser treatment will be deferred and reassessed at the subsequent laser evaluation visit. Focal laser treatment and focal laser re-treatment will be administered no more than once every 90 days.

Focal laser therapy will be applied to all leaking microaneurysms on fluorescein angiography. Focal laser therapy will not be applied if significant macular ischemia is present involving the foveal avascular zone (once this has been determined additional fluorescein angiography and focal laser treatment planning should not be performed as the subject will no longer be eligible for focal laser treatment). Focal laser will also not be applied if treatment is considered too close to the foveal avascular zone or to macular edema not related to DME (cystoid

macular edema, etc.). If no microaneurysms are present on fluorescein angiography, then focal laser therapy should be deferred and reassessed with repeat fluorescein angiography at the first visit that occurs after 90 days.

GILA Cohort (60 eyes) – Monthly intravitreal injections of 0.3 mg ranibizumab for four visits combined with GuIded LAser (GILA) photocoagulation to all microaneurysms in the area of DME at the second visit (Week 4). Fluorescein angiography is to be repeated approximately every 3 months (the first visit that occurs ≥ 90 days from the preceding fluorescein angiography visit). Guided laser will be repeated at those visits if leakage is present from microaneurysms. If the central foveal thickness is $\leq$ 325 μm at the fourth visit (Week 12), eyes will receive 0.3 mg ranibizumab and the extension phase will begin. For all subsequent visits in the extension phase, appropriate changes to the treatment interval with 0.3 mg ranibizumab (i.e. extend, maintain, reduce) will be made based on pre-specified SD-OCT criteria. Treatment is rendered at every visit, no earlier than 7 days before the target date and no later than 7 days after the target date, but the time between visits is individualized based on each subject's response to treatment. If the central foveal thickness is > 325 μm at week 12, then the patient will continue to receive monthly intravitreal injections of 0.3 mg ranbizumab and possible guided laser every 3 months until the central foveal thickness is $\leq$ 325 μm. Once the central foveal thickness is $\leq$ 325 μm, then the study eye will begin the extension phase of the study.

Starting at week 104, study eyes will have the opportunity to undergo treatment on a pro re nata (PRN) basis. Thus, eyes who have a central subfield thickness (CST) ≤ 325 microns at the week 104 visit, will not be given treatment at week 104. Starting at week 104, eyes will be seen every 4 weeks and will be given an intravitreal injection of ranibizumab 0.3 mg only if the CST is > 325 microns. Eyes will also receive treatment if there is a > 5 letter loss due to DME (compared to the vision at week 104), regardless of thickness on OCT.

After week 104, subjects will be evaluated for focal laser treatment in the same manner as the Monthly and TREX Cohorts. Subjects will be evaluated for focal laser treatment at week 116, week 128, week 140, and week 152. If the subject has received $\geq$ 2 intravitreal injections of ranibizumab within the prior 90 day period, then fluorescein angiography will be performed and focal laser treatment will be applied to any leaking microaneurysms. If the patient does not meet this criteria for focal laser treatment, then fluorescein angiography and focal laser treatment will be

deferred and reassessed at the subsequent laser evaluation visit. Focal laser treatment and focal laser re-treatment will be administered no more than once every 90 days.

Focal laser therapy will be applied to all leaking microaneurysms on fluorescein angiography. Focal laser therapy will not be applied if significant macular ischemia is present involving the foveal avascular zone (once this has been determined additional fluorescein angiography and focal laser treatment planning should not be performed as the subject will no longer be eligible for focal laser treatment). Focal laser will also not be applied if treatment is considered too close to the foveal avascular zone or to macular edema not related to DME (cystoid macular edema, etc.). If no microaneurysms are present on fluorescein angiography, then focal laser therapy should be deferred and reassessed with repeat fluorescein angiography at the first visit that occurs after 90 days.

- End-Point Visits

  Subjects will continue to receive study treatments according to the above treatment protocol until week 104. A “Hard End-Point Visit” will occur at week 52, week 104, and week 156. A “Biologic End-Point Visit” will occur 4 weeks after the previous injection near the 12-month time point (week 46 – week 57),24-month time point (week 92 – week 107), and 36-month time point (week 156). Only best corrected visual acuity and SD-OCT measurements will be recorded at these endpoint visits. No study treatment will be given at these end-point visits, unless the patient has a regular study treatment visit at these time points.

  Study eyes which have not met criteria allowing them to extend to at least 6 weeks for two consecutive visits by the week 52 hard endpoint visit will receive a series of three intravitreal injections of ranibizumab 0.3 mg every 4 weeks regardless of OCT measurement, beginning at week 52 if treatment is indicated at that time or the first treatment visit thereafter. The study eye will resume treatment interval determinations based on the pre-specified criteria at the time of the third monthly intravitreal injection.

  Fellow eyes not enrolled into a study group and that have DME during the course of the study may be treated with standard of care macular laser photocoagulation and/or intravitreal injections of 0.3 mg of ranibizumab at the Investigator’s discretion. Ranibizumab will be provided by Genetech for treatment of DME in the fellow eye.

4.3 STUDY TREATMENT

4.3.1 Formulation

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile, 3-mL stoppered glass vial. Each single-use vial is designed to deliver 0.05 mL of 6-mg/mL ranibizumab aqueous solution with 10 mM histidine HCl, 10%, α-trehalose dihydrate, and 0.01% polysorbate 20, pH 5.5. This results in the delivery of a 0.3 mg dose of ranibizumab. 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

Patient will be to receive intravitreal injections of 0.3 mg of ranibizumab.

b. Administration

* *See Appendix B for detailed preparation and administration of ranibizumab injection.

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 except non-ranibizumab intraocular therapies for DME, including corticosteroids and other anti-VEGF agents.

4.5 STUDY ASSESSMENTS

4.5.1 Assessments during the Treatment Period

See the table of events for the exact assessments at each visit.

Vital Signs (All Study Visits)

Vital signs will include measurements of pulse and systolic and diastolic blood pressure while the patient is in a seated position. Vital signs should be taken before injection of study drug.

Ocular Assessments (All Study Visits)

- Best Corrected Visual Acuity Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985) at 4 meters. After week 104, a new manifest refraction will be performed at week 116, week 128, week 140, and week 156. The pre-existing refraction will be used to test visual acuity at 4 meters in the intervening visits between weeks 104 and week 156.
- IOP measurement- (perform prior to dilating eyes and post intravitreal injection; the method used for a patient must remain consistent throughout the study). IOP may be measured either by TonoPen or applanation tonometry, but the method of measurement must remain consistent for each patient throughout the study.
- Slit lamp examination- Patient's anterior eye structure and ocular adnexa will be examined at each study visit using a slit lamp by the investigator.
- Indirect Ophthalmoscopy- The patient's posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre dose (bilateral) by the investigator

Ocular Imaging

Fundus Photography and Fluorescein Angiography (FA)

The anatomical state of the retinal vasculature of the study eye will be evaluated by funduscopic examination, fundus photography and FA. Fundus photography and Fluorescein angiography will be done in the Monthly and TREX Cohorts at baseline (screening visit) and again at week 12, month 12,month 24, and month 36. Fundus photography and fluorescein angiography will be done in the GILA Cohort at baseline (screening visit), and again at week 4, and then approximately every three months (first visit that occurs > 90 days from previous fluorescein angiogram). See Appendix A. Fluorescein angiography will be used to guide focal laser treatment for all treatment cohorts at week 116, week 128, week 140, and week 152 if laser treatment criteria has been met.

Optical Coherence Tomography (All Study Visits) –

Ocular morphology will be evaluated using the Heidelberg Spectralis Domain (SD) OCT on the study eye. All SD-OCT images will be captured using the

most current software. All SD-OCTs will be electronically archived at the site as part of the source documentation.

Microperimetry –

Microperimetry will be performed at the locations where a microperimeter is available on all study eyes in the TREX and GILA cohorts at screening, week 24, week 52 and week 104, or the closest visit to these time points.

4.5.2 Early Termination Assessments

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

4.6 SUBJECT DISCONTINUATION

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

The subject may be withdrawn from the study for any reason: if it is in the best interest of the subject, intercurrent illness, adverse events, or worsening condition. Palmetto Retina Center, LLC or John F. Payne, 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 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

Palmetto Retina Center, LLC or Genentech may terminate this study at any time. Reasons for terminating the study may include the following:

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

4.8 STATISTICAL METHODS

4.8.1 Analysis of the Conduct of the Study

The analysis of complete data (36-month treatment period) for the study will be performed when all patients have either completed the visit at month 36 or discontinued early from the study, all data collected from the study are in the database, and the database is locked.

Interim analysis of data from the 12-month period will be performed when all patients have either completed the visit at month 12 or discontinued early from the study. Treatment assignment will be unmasked to the personnel performing the analysis when all data collected through month 12 are in the database and the data have been cleaned and verified. The Peto group sequential procedure (Z +/- 3.0 at all interim analyses) will be used to control for the possibility of type I error arising from the 12 month interim analysis.

For the primary objective, power calculations for different margins were undertaken. Familywise alpha of 0.05 was divided equally among three TOST (two one sided test) procedures (alpha=0.0167): (1) comparing TREX vs. GILA in the 60 patients enrolled with bilateral disease, (2) TREX vs. control (total n=90, controls n=30), and (3) GILA vs. control (total n=90, controls n=30). A standard deviation of 11 letters was used for the power calculations and based from the RISE/RIDE data for subjects with DME. The power calculations suggests that the minimum boundary of equivalence for TREX vs. GILA that we can demonstrate is +/- 7 letters (less than two lines of vision) and +/- 9 letters (less than two lines of vision) for TREX and GILA vs. controls. Paired sample t-test will be used to compare TREX vs. GILA and two sample t-test will be used to compare the two groups vs. controls.

Because of the potential for confounding of the effect when comparing the control group (monthly cohort) to the TREX and GILA groups, we will use linear regression modeling with change in ETDRS as outcome

and cohort as main effect controlling for potential confounders (e.g., age, race, sex).
Adverse events, number of injections, and number of office visits will be approached statistically with descriptive analyses with point estimates and confidence limits provided. Exploratory linear, logistic, and time-to-event models will be used to analyze the other secondary outcomes.

4.8.2 Safety Analyses

Any adverse events, laboratory assessments, physical examinations, vital signs, ocular examinations and measurements from all 150 eyes will be utilized to summarize safety data for this study.

- Incidence and severity of adverse events (ocular and non-ocular).

4.8.3 Efficacy Analyses

Primary Endpoint

- Mean change in ETDRS visual acuity at 24 months (week 92 – week 107) from Day 0.

Secondary Endpoints

- Incidence and severity of adverse events (ocular and non-ocular).
- Total number of intravitreal injections required during each year of the study period. In a separate proof of concept analysis, the number of intravitreal injections in the TREX and GILA cohorts over the 36-month study period will be compared with that of the other two cohorts ($p = 0.20$)
- Total number of office visits and imaging studies performed during each year of the study period (week 52, week 104, and week 156).
- Mean change in central foveal thickness per SDOCT from randomization to 12 months (week 46 – week 57),randomization to 24-months (week 92 – week 107), and randomization to 36 months (week 156)..
- Percentage of eyes gaining or losing 3 lines of vision or more and 1 line of vision or more at 6 months (week 22 – week 29),12 months (week 46 – week 57),18 months (week 70 – week 85),24 months (week 92 – week 107), and 36 months (week 156) from Day 0.
- Noninferiority comparison (margin of 9 letters) of mean change in ETDRS vision from Day 0 to 24 months (week 92 – week 107) between the three study groups.

- The percentage of eyes which show progression of proliferative diabetic retinopathy requiring panretinal photocoagulation and/or pars plana vitrectomy over the 36-month study period.

- The percentage of eyes in the TREX and GILA cohorts who are eligible to begin the extension phase after 4 treatment visits.

- For TREX and GILA Cohorts, the time to achieve a “Secondary or Tertiary Baseline” retinal thickness.
- Percentage of eyes in each cohort that have shown a two-step change (increase and decrease) in diabetic retinopathy at 24 months and 36 months from day 0.

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. SAFETY REPORTING OF ADVERSE EVENTS

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 Lucentis, 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 DME 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.

Pre-existing 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 and ends 30 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 Lucentis (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 Lucentis, 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 Lucentis; and/or the AE abates or resolves upon discontinuation of the Lucentis or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the Lucentis (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to Lucentis administration (e.g., cancer diagnosed 2 days after first dose of Lucentis).

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 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

5.4.1 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?”

5.4.2 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, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

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. Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing 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 pre-existing 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 Lucentis, 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 Lucentis 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 Lucentis 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.

The Lucentis Events of Special Interest are:

- Endophthalmitis
- Intraocular inflammation (including vitritis and uveitis)
- Cataract (Traumatic)
- Increased IOP
- ATEs including stroke
- Retinal Pigment Tear
- Retinal Detachment

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 Lucentis 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 Lucentis 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 Lucentis 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.

5.4.3 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

5.4.4 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

5.4.5 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 Lucentis. An unexpected adverse event is one that is not already described in the Lucentis 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 Lucentis. An unexpected adverse event is one that is not already described in the Lucentis 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

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 Clinical Operations contact for the study:

E-mail: lucentisgsr_coa-d@gene.com
Fax: 866-728-4622

Genentech
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5.4.6 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 Palmetto 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 Palmetto 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 Palmetto 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 Palmetto 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 Palmetto 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 Fax: 1-866-551-1893

7.0 REFERENCES

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APPENDIX A
Study Flowchart

The study flowchart will be sent as a separate document.

APPENDIX B

Pre-Administration,, Administration, and Post-Administration 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). Clinic staff will observe aseptic technique involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration. In addition to the procedures outlined below, added safety measures in adherence to specific institutional policies associated with intravitreal injections will be observed.

The technician assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4x4 sterile pads, pack of sterile cotton-tipped applicators, eyelid speculum, 0.5% proparacaine hydrochloride, 1 or 2% lidocaine(without epinephrine) for subconjunctival injection (at investigator's discretion), ophthalmic antimicrobial solution (e.g. trimethoprim-polymyxin B ophthalmic solution, ofloxacin ophthalmic solution, ophthalmic gatifloxacin solution, ophthalmic moxifloxacin solution), and injection supplies

Pre-Administration

- Instill 2 drops of 0.5% proparacaine hydrochloride into the study eye, followed by 2 drops of a broad-spectrum antimicrobial solution (e.g. trimethoprim-polymyxin B ophthalmic solution, ofloxacin ophthalmic solution, ophthalmic gatifloxacin solution, ophthalmic moxifloxacin solution).
- Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Make certain that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.
- The investigator will glove, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill 2 drops of 5% povidone iodine ophthalmic solution in the study eye, making sure the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.
- Saturate a sterile cotton-tipped applicator with 0.5% proparacaine hydrochloride drops and hold the swab against the planned intravitreal injection site for 10 seconds in preparation for the subconjunctival injection of 1 or 2% lidocaine hydrochloride ophthalmic solution for injection (without epinephrine).
- Use a sterile 4×4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.

- Instruct subject to direct gaze away from syringe prior to ranibizumab injection.

Administration of Intravitreal Injection

- Using aseptic technique, all of the ranibizumab vial contents are withdrawn through a 5 µm, 19g filter needle attached to a 1cc tuberculin syringe.
- The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection.
- Replace the filter needle with a sterile 30g, ½" needle for the injection
- Expel the contents of the syringe until the plunger tip is aligned with the line that marks 0.05mL.
- Administer intravitreal injection through the pars plana either inferiorly or superiorly from a temporal approach, 3.5-4 mm posterior to the corneal scleral limbus.
- As the needle is withdrawn, a sterile cotton-tipped applicator is rolled over the injection site.

Post-Administration

- Instill broad spectrum antibiotic at the injection site.
- Thoroughly rinse the treated eye with sterile ophthalmic solution.
- Confirm adequate retinal perfusion by either indirect ophthalmoscopy or evaluating subject's ability to see from the study eye (investigator's discretion).
- Measure intraocular pressure (IOP) 30 minutes (± 15 minutes) after the injection. Subject will continue to be monitored until IOP is ≤30 mmHg.
- Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Should a site's injection procedure differ from above they may submit to sponsor for approval.

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. The responsible principal investigator should write this section.

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

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

MCN	Reported Event	Submission Date

Or

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

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

Assessment of Relationship

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

Based on review of available data, Palmetto 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

Based on review of available data, the Palmetto 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

Based on review of available data, the Palmetto 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 Palmetto 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.