

## PROTOCOL

STUDY TITLE: A phase IIIb, multicenter, randomized, controlled study of the safety, tolerability and efficacy of intravitreal injections of 0.5mg ranibizumab given monthly compared to a Treat and Extend protocol in patients with wet age-related macular degeneration (T-REX)

STUDY DRUG Ranibizumab

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## **1. BACKGROUND**

### **1.1 PATHOPHYSIOLOGY**

Neovascular AMD is typically characterized by choroidal neovascularization (CNV) in the macular region. The choroidal capillaries and associated collagenous matrix proliferate and penetrate Bruch's membrane to form a fibrovascular "membrane" external to the retinal pigment epithelium (RPE), which may then extend through the RPE into the subretinal space. In some cases, however, the presence of an apical/subretinal fibrovascular membrane is not accompanied by a fibrovascular lesion on the basolateral/choroidal side of the RPE. Moreover, in some cases of neovascular AMD, there is strong angiographic evidence that the new vessels are supplied from the retinal circulation rather than from the choroidal circulation. The increased permeability of the newly formed capillaries can lead to accumulation of serous fluid or blood under the RPE or between the RPE and the sensory retina. If the center of the macula becomes detached, central vision is impaired. Retinal hemorrhage or involution of the new vessels is accompanied by fibrous metaplasia and organization that can result in an elevated subretinal mass called a disciform scar (D'Amico 1994).

The stimuli that produce CNV are unknown. However, there is strong evidence suggesting that angiogenic factors, such as vascular endothelial growth factor (VEGF), play a role in the pathogenesis of AMD (Eyetechnology Study Group 2003; Rosenfeld 2006, Brown 2006).

### **1.2 TREATMENT OF AGE RELATED MACULAR DEGENERATION**

The T-REX trial will address patients with treatment naive wet age-related macular degeneration (AMD).

The introduction of pharmaceuticals that target VEGF-A revolutionized the management of wet AMD. VEGF-A is a diffusible cytokine that stimulates angiogenesis and vascular permeability. Clinical blockage by intravitreal injection of biological agents such as ranibizumab, bevacizumab and aflibercept is well tolerated and remarkably effective against choroidal neovascularization (CNV) in AMD patients.

### **1.3 RANIBIZUMAB AND AGE RELATED MACULAR DEGENERATION**

Such efficacy was initially demonstrated with ranibizumab in two landmark trials, MARINA and ANCHOR (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD and Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD). For the first time, patients with CNV secondary to AMD experienced an average visual improvement with over 90% of eyes losing less than 15 letters and about 30% of eyes gaining significant vision. Ranibizumab was FDA approved on June 30, 2006.

## **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 7-8 days. Repeated intravitreal injections of ranibizumab can lead to detectable antibodies in serum in rabbits and cynomolgus monkeys.

### **1.4.2 Nonclinical Toxicology**

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

### **1.4.3 Nonclinical Data Supporting the Anti-Edema Activity of Ranibizumab**

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

## **1.5 Clinical Experience With Ranibizumab**

Ranibizumab has been or is being studied in more than 5000 subjects with neovascular AMD in a number of Phase I, I/II, II, III, and IIIb clinical trials. Ranibizumab is contraindicated in patients with ocular or periocular infections and in those with known hypersensitivity to ranibizumab or any of the excipients in ranibizumab. Intravitreal injections, including those with ranibizumab, have been associated with endophthalmitis and retinal detachment. Proper aseptic injection technique should always be used when administering ranibizumab. Increases in IOP have been noted within 60 minutes of intravitreal injection with ranibizumab. Therefore, IOP as well as perfusion of the optic nerve head should be monitored and managed appropriately. Serious adverse events related to the injection procedure have occurred in <0.1% of intravitreal injections include endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract. Other serious ocular adverse events observed among ranibizumab-treated subjects and occurring in <2% of subjects included intraocular inflammation

and increased IOP. The most common adverse reactions (reported  $\geq 6\%$  higher in ranibizumab-treated subjects than control subjects) were conjunctival hemorrhage, eye pain, vitreous floaters, increased IOP, and intraocular inflammation.

Although there was a low rate ( $<4\%$ ) of arterial thromboembolic events (ATEs) observed in the ranibizumab clinical trials there is a potential risk of ATEs following intravitreal use of inhibitors of VEGF. The rate of ATEs in three studies (FVF2598g, FVF2587g, and FVF3192g) in the first year was 1.9% of subjects in the combined group of subjects treated with 0.3 mg or 0.5 mg ranibizumab compared with 1.1% of subjects in the control arms of the studies. In the second year of Study FVF2598g and FVF2587g, the rate of ATEs was 2.6% of subjects in the combined group of those treated with 0.3 mg or 0.5 mg ranibizumab compared with 2.9% of subjects in the control arm. The most common non-ocular adverse reactions observed in  $\geq 15\%$  of ranibizumab-treated subjects that occurred more frequently than in control subjects included, nasopharyngitis, headache, and upper respiratory tract infection.

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

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

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

Ranibizumab was well tolerated, and the incidence of ocular SAEs and AEs was low and unrelated to dose. The rates of individual key ocular SAEs in Cohort 1 were  $< 1\%$  and were similar across dose groups. Endophthalmitis or presumed endophthalmitis developed in 0.2% subjects in the 0.3-mg group and 0.4%

subjects in the 0.5-mg group. The incidence of ocular inflammation, including iritis, uveitis, vitritis, and iridocyclitis was 1.9% in the 0.3-mg group and 1.5% in the 0.5-mg group. Overall cataract rates were 5.4% (0.3 mg) and 6.0% (0.5 mg) and were similar when broken down by nuclear, subcapsular, and cortical subtypes. The rates of individual key ocular SAEs in Cohort 2 were <1%.

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

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

## **2. Objectives**

This trial will assess the safety, tolerability and efficacy of a treat and extend management protocol for wet age related macular degeneration (AMD). Subjects will be randomized, 1:2, 1 (control arm-Cohort A) to 2 (comparator, treat and extend- Cohort B). Subjects in the control arm will receive monthly intravitreal injections of 0.5mg ranibizumab for 104 weeks and then be treated PRN for another 52 weeks. Subjects in the controlled arm will receive 3 monthly (visits 2, 4 and 5) intravitreal injections of 0.5mg ranibizumab followed by a treat and extend protocol. In a treat and extend protocol length between visits are increased by 2-week intervals, when there is no evidence of exudative disease activity present on ophthalmic exam or spectral-domain (SD)-OCT. In the treat and extend arm, the interval between injections will not exceed 12 weeks; specifically, subjects who are in the treat and extend Cohort B and do not exhibit exudative activity either by SD-OCT or clinical examination will receive mandatory study drug injection every twelve weeks. Subjects will receive intravitreal injections of 0.5mg ranibizumab at every scheduled visit from Day 0 to week 103. At week 104 all subjects will be seen, subjects who have reached the 12 week interval will be seen monthly and treated PRN. Subjects who have not achieved the 12-week interval, at week 104, will continue a treat and extend protocol until the 12 week interval is met. Once those subjects reach a 12 week interval, at any time during week 104 to week 156, they will then switch to monthly visits and treated PRN.

### **2.1 Primary Objective**

- Mean change in ETDRS visual acuity from baseline to weeks 24-28, baseline to weeks 48-56, baseline to weeks 72-82, baseline to week 104, baseline to weeks 128-132 and baseline to week 156.

## 2.2 Secondary Objectives

- Incidence and severity of adverse events (ocular and non-ocular).
- Total number of intravitreal injections required from baseline through weeks 48-57 (week closest to week 52), baseline through week 104 and baseline through week 156.
- Total number of office visits and imaging studies performed from baseline through weeks 24-28 (week closest to week 26), baseline through weeks 48-56 (week closest to week 52), baseline through weeks 72-82 (week closest to week 78), baseline through week 104, baseline through weeks 128-132 (week closest to week 132) and baseline through week 156.
- Percentage of subjects with persistent active exudation on SD-OCT from baseline through weeks 48-57 (week closest to week 52), baseline through week 104 and baseline through week 156.
- Percentage of subjects with persistent leakage on fluorescein angiography from baseline through weeks 24-28, baseline to weeks 48-56, baseline to weeks 72-82, baseline to week 104, baseline to weeks 128- 132 and baseline to week 156.
- CNVM lesion size at baseline, compared to baseline to weeks 24-28, baseline to weeks 48-56, baseline to weeks 72-82, baseline to week 104, baseline to weeks 128-132 and baseline to week 156, as determined by fluorescein angiography.
- Mean change in central foveal thickness by SD-OCT from baseline to weeks 48-57, baseline to week 104 and baseline to week 156.
- Mean change in BCVA by ETDRS letter score from baseline through weeks 24-28, baseline through weeks 48-56, baseline through weeks 72-82, baseline to week 104, baseline through weeks 128-132 and baseline to week 156.

### Endpoint Visits:

Few completed prospective trials have employed a treat and extend protocol. Therefore, there is little data regarding optimal endpoint usage. These endpoints will allow comparison of data from each cohort.

1. **Floating Endpoints** (also known as the Biological Endpoints): Analyses will be performed between weeks 24-28, between weeks 48-57, between weeks 72-82, week 104, between weeks 128-132 and week 156 (range to be determined by timing of last injection). If more than one possible endpoint exists, the time point closest to week 26, week 52, week 78, week 104, week 130 or week 156 will be used. This will be applied to both Cohort A and B, but

likely to be most important for Cohort B. All endpoints are measured 4 weeks following the last injection.

2. **Hard Endpoints:** analyses will be performed at week 52 (day 365± 7 days), week 104 (day 730 ± 7 days) and week 156 (day 1095 ± 7 days).

### **3. STUDY DESIGN**

#### **3.1 DESCRIPTION OF STUDY**

TREX is a phase IIIb, multicenter, randomized, controlled clinical study. Subjects will be randomized 1:2 to “monthly” (control arm) or “treat and extend” protocol (comparator arm) respectively. TREX assess the safety, tolerability and efficacy of intravitreal injections (IVT) of 0.5mg ranibizumab given monthly for up to 100 weeks followed by pro re nata (PRN) treatment for 56 weeks compared to a Treat and Extend protocol for 156 weeks in patients with wet age-related macular degeneration (AMD). Subjects treated in a treat and extend protocol receive 3 consecutive IVT 0.5 mg ranibizumab (visits 2, 4 and 5). Starting at week 8, if a subject has achieved a “dry” macula; signs of active exudation have resolved will begin a Treat and Extend protocol (visits lengthened by 2 week intervals every visit a dry macular is maintained). At the beginning of the 104-week endpoint subjects initially randomized to the TREX cohort will transition to PRN re-treatment when there is no exudative disease activity at the 12-week interval.

#### **3.2 OVERVIEW OF STUDY DESIGN**

This trial will compare the results of 2 cohorts, with different treatment intervals, to assess the safety, tolerability and efficacy of IVT of ranibizumab for the treatment of wet AMD. Specifically, this trial will evaluate the ability to reduce the amount of visits and IVT ranibizumab treatments needed all while maintaining an exudation-free macula. Subjects in both cohorts will be followed for a total of 156 weeks.

**Cohort A** (control arm, monthly, n=20) Subjects will receive monthly treatment of IVT 0.5 mg ranibizumab from Day 0 to week 100. Monthly treatment is defined as every 28 days (±7 days). Dosing should not occur earlier than 21 days after the previous treatment.

#### **Week 104 – Week 156**

Starting at week 104 subjects will be seen monthly and treated with IVT ranibizumab pro re nata (PRN) based on pre-defined re-treatment criteria.

#### **Retreatment criteria for PRN phase**

Re-treatment will be initiated if any of the following criteria are meet:

- Presence of any abnormal intraretinal or subretinal fluid on high resolution SD-OCT.

- Presence of new intraretinal or subretinal hemorrhage related to AMD on examination.
- 10 letter loss from previous visit, related to active wet AMD in the opinion of the treating investigator

**Cohort B** (comparator arm, TREX, n=40) Subjects will receive a minimum of 3 consecutive IVT 0.5 mg ranibizumab (visits 2, 4 and 5). Starting at week 8, if a subject has achieved a “dry” macula; signs of active exudation have resolved by both ophthalmic exam and SD-OCT evaluation they will begin a Treat and Extend protocol.

For a macula to be considered “dry” it must meet both the following criteria:

1. Resolution of intraretinal and subretinal fluid
2. Resolution of all subretinal hemorrhage related to active exudative AMD

Resolution of pigment epithelial detachments (PED) is not required for a macula to be considered “dry”. Small intraretinal cystic areas observed on SD-OCT are acceptable and the corresponding macula can be considered dry. The criteria for these are specific; see reference images (Appendix D) for examples of acceptable intraretinal cystic spaces. When cysts described in Appendix D are present the macula should be considered dry and should be noted on the SD-OCT interpretation. Also, minimal increased retinal thickening on SD-OCT without definitive intraretinal or subretinal exudative fluid can be observed and the corresponding macula will be considered dry.

Once a “dry” macula is achieved the interval between visits is then lengthened by 2-week increments, at every visit the macula is “dry”. IVT ranibizumab will be rendered at every visit, no earlier than 7 days before the target date and no later than 7 days after the target date; the interval between visits is individualized based on each patient’s response to treatment. The interval between injections will not exceed 12 weeks

After a subject is extended beyond 4-weeks and develops recurrent exudative disease activity, the eye is treated and the treatment interval for the next visit is reduced by 2 weeks, compared to the previous treatment interval. The interval between treatments will be reduced by 2-week intervals until a dry macula is again established. Once a dry macula is again achieved, the interval between visits will be extended by 1-week intervals, instead of 2-week intervals.

For example: If recurrent exudative disease activity is detected after an 8-week interval, the eye is treated and the interval for the next visit is reduced to 6 weeks; if the macula is then dry after the 6-week interval, the interval is increased to 7 weeks. If the macula is then dry after the 7-week interval, the interval is increased to 8 weeks, etc.

Once an eye is extended by 1-week intervals, if recurrent exudative disease is detected again, the treatment interval for the next visit is reduced by 1

week, compared to the previous treatment interval, and will continue to be decreased by 1-week intervals until dry or the 4-week interval is reached. Once a dry macula is again established, the most recent interval between treatments is maintained for one additional visit; if the macula remains dry at this time, the interval will then be extended by 1-week increments.

If an eye exhibits recurrent exudative disease three times at a given interval and is unable to extend beyond that interval, the eye will continue treatment at the next shorter interval for 3 consecutive visits. Once the macula has achieved a "dry" status again the treat and extend protocol will re-start, the interval between visits will be lengthened by 1-week increments, at every visit the macula is "dry". If the subject exhibits recurrent exudative disease again the interval will be decreased, the treatment interval for the next visit is reduced by 1 week, compared to the previous treatment interval, and will stay at that interval for 3 consecutive visits before extending by 1 week again.

#### **Evidence of recurrent exudative activity**

Clinical evidence of recurrent exudative disease activity requiring reducing the interval between treatments includes any of the following:

1. Evidence of subretinal or intraretinal fluid on SD-OCT which is *not* classified as small intraretinal cystic areas unrelated to active exudative AMD (Appendix D) or minimal increased retinal thickening by SD-OCT without definitive intraretinal or subretinal fluid
2. New macular hemorrhage related to active exudative AMD.
3. ETDRS VA loss of 5 letters from the previous measurement due to neovascular AMD disease process with corresponding SD-OCT evidence of fluid in the macula.
4. Increase in CRT of 50 microns due to active exudative AMD.

The isolated presence of a PED, or enlargement of a PED, does not constitute evidence of exudative disease activity.

If an eye has an ETDRS VA decrease of  $\geq 4$  lines (20 letters) or a subretinal macular hemorrhage of 1DD or larger, at any point during the trial, the subject will subsequently be treated with ranibizumab every 4 weeks.

#### **Week 104 – Week 156**

Starting at Week 104 subjects who have achieved a "dry" macula, at the 12 week interval will be seen monthly and treated pro re nata (PRN) based on pre-defined re-treatment criteria. Study visits should be scheduled to occur every 28 ( $\pm 7$ ) days relative to the date of week 104 visit.

### **Retreatment criteria for PRN phase**

Re-treatment will be initiated if any of the following criteria are met:

- Presence of any abnormal intraretinal or subretinal fluid on high resolution SD-OCT.
- Presence of new intraretinal or subretinal hemorrhage related to AMD on examination.
- 10 letter loss from previous visit, related to active wet AMD in the opinion of the treating investigator

Starting at Week 104, subjects who have NOT achieved extension to the 12-week treatment interval will continue with the treat and extend protocol. At any time during weeks 104 to 156 if a subject achieves a "dry" macula, at the 12-week interval, they will immediately begin monthly PRN treatment based on pre-defined re-treatment criteria. Study visits should be scheduled to occur every 28 ( $\pm 7$ ) days, relative to the date the 12-week interval is achieved. Subjects will not be treated at the visit they achieve the 12 week interval (this is the date PRN treatment will begin).

### **3.3 Rationale For Study Design**

Pharmaceutical agents that target VEGF have revolutionized the management of neovascular AMD. VEGF-A is a diffusible cytokine that stimulates angiogenesis and vascular permeability. Clinical blockade by intravitreal injection of ranibizumab is remarkably effective against choroidal neovascularization (CNV) in AMD patients.

The efficacy of anti-VEGF therapy in AMD was initially demonstrated with the modified antibody fragment ranibizumab in two landmark trials, ANCHOR and MARINA. For the first time, patients with CNV secondary to AMD experienced an average visual improvement with over 90% of eyes losing less than 15 letters and about 30% of eyes gaining significant vision. Ranibizumab was FDA approved on June 30, 2006.

Since then we have learned a tremendous amount about the clinical utility of intraocular VEGF blockade. Despite these advances, a major clinical controversy regarding exudative AMD management remains today: what is the optimal treatment approach to maximize visual outcome and minimize treatment burden for patients and the health care system?

#### **Monthly vs Extended Fixed Interval Schedules vs PRN Treatment**

Both MARINA and ANCHOR employed monthly ranibizumab dosing. While this treatment approach yielded exceptional results with sustained visual gains over 2 years, monthly doctor visits are often impractical and difficult for patients and their caregivers. Therefore, large prospective trials have evaluated 2 main alternative treatment approaches in an attempt to decrease the treatment burden while maintaining visual gains: fixed interval treatments with less than monthly dosing, and pro re nata (PRN) treatment.

Prior attempts at fixed interval schedules employing less than monthly treatments have resulted in disappointing visual outcomes. For example the PIER study, a phase IIIb, multicenter, randomized, controlled trial compared sham injections to ranibizumab monthly for 3 months and then quarterly<sup>4</sup>. In stark contrast to the results of MARINA and ANCHOR, while visual outcomes were statistically better than the sham treated control group, the visual acuity improvement observed at month 3 was lost by month 12, with patients losing a mean of -1.6, and -0.2 letters in the 0.3 mg and 0.5 mg ranibizumab groups respectively. Similarly suboptimal outcomes were seen with the EXCITE and SAILOR results which employed similar quarterly dosing strategies without success.

Importantly, however, subgroup analysis of PIER patients who showed no recurrence of exudative disease activity after the first 3 months of treatment on quarterly dosing showed sustained visual gains compared to visual losses observed in patients who showed persistent exudative disease activity after the first 3 months of treatment (Brown D.M. et al RETINA. In press). It is likely that the prolonged and recurrent episodes of retinal edema observed in the majority of under-treated quarterly treated patients directly contributed to their poor visual outcomes. Therefore, it seems that while under-treatment of active exudative disease in the setting of wet AMD leads to suboptimal visual outcomes, not all patients require monthly dosing to achieve optimal visual outcomes; namely, those wet AMD patients without active exudative disease may be able to have a reduced treatment burden while maintaining their visual gains.

In comparison to fixed extended dosing, some strict prospective studies of PRN treatment approaches have yielded positive results that have appeared to be in the range of vision gains demonstrated in the MARINA and ANCHOR established standard. PrONTO was a 2-year, prospective, open label, non-comparison single arm study of 40 eyes, in which patients received 3 consecutive monthly intravitreal injections of ranibizumab followed by monthly evaluation and retreatment if certain clinical criteria were fulfilled<sup>7</sup>. At month 24, mean visual acuity improved 11.1 letters with an average of 9.9 injections. One of the important observations from PrONTO was the wide range of necessary injections among patients; 3 patients required only the minimum possible number of treatments, 3; and 2 patients required the maximum possible number of injections, 24.

In the much larger and prospectively randomized CATT trial, analysis of pooled data including both ranibizumab and bevacizumab treated eyes suggested that monthly fixed dosing may be preferable to PRN therapy. In respect to avoiding vision loss the best performing group (monthly ranibizumab) had 7% 3-line losers from baseline compared to the worst (as needed bevacizumab), which experienced 12% 3-line losers. The vision losses seen with PRN therapy may be secondary to PRN regimen's decreased

anatomic efficacy, which led to more persistent retinal fluid compared to monthly treatment (75%-85% vs 52-67%,  $P < 0.0001$ ) and an increase in baseline CNVM lesion size by 1.9 to 3mm<sup>2</sup> vs -0.4 to 1.6mm<sup>2</sup> with monthly treatment ( $P = 0.0003$ ). Also emphasizing the challenges of PRN dosing, half of patients initially assigned to monthly treatment were reassigned to PRN treatment after 1 year; these re-assigned PRN patients lost between 1.5 and 3 mean letters more than the patients who maintained monthly dosing ( $P = 0.03$ ).

Similarly, results of the phase III, multicenter, randomized controlled HARBOR trial also supported the superiority of monthly fixed dosing compared to strict monthly monitoring with PRN treatment. While both the 0.5mg and 2.0mg ranibizumab PRN arms resulted in clinically meaningful improvements in vision, neither arm met the prespecified primary endpoint of statistical noninferiority compared with 0.5mg ranibizumab monthly injections.

### **Treat and Extend Treatment**

Just as every human is genetically distinct, so too it appears is the clinical response to anti-VEGF treatments in the setting of wet AMD, underscoring the concept of individualized dosing regimens. Supporting this concept, intraocular levels of VEGF vary among patients with phenotypically similar diseases over a wide range of diagnoses.

A treat and extend protocol starts with monthly injections until signs of exudation have resolved with clinical and SD-OCT confirmation. The interval between visits is then sequentially lengthened by 1 to 2 weeks as long as there are no signs of recurrent exudation. Treatment is rendered at every visit but the time between visits is individualized based on a patient's response to treatment. When recurrent disease is detected, the treatment interval is reduced. The goal is to maintain an exudation-free macula with the fewest number of office visits, tests and injections.

Such a protocol was first described in 2007. Since then, four reports have described retrospective analyses of patients treated with varying types of treat and extend protocols. For example, Gupta et al reported a retrospective analysis of 92 eyes with wet AMD treated with ranibizumab according to a treat and extend protocol. After a mean follow-up of 1.5 years, non-refracted visual acuity outcomes demonstrated 32% of patients gaining 3 lines of Snellen visual acuity and 96% of patients losing less than 3 lines of vision. Similar to the variability of required treatments reported in PrONTO a wide range of required treatment frequencies was observed. After an exudation-free macula was achieved, 42 eyes (46%) demonstrated no recurrent exudation while 7 eyes (8%) showed persistent exudation at every visit, requiring monthly dosing throughout the study period. These retrospective studies consistently report beneficial outcomes; however evaluations, follow-up intervals and endpoints were not standardized or consistent.

Most visual acuity data have shown that monthly dosing produces superior anatomic and visual acuity outcomes compared to both fixed interval dosing employing less than monthly treatments and monthly visits with PRN treatment upon detection of exudative disease activity. Nonetheless, individualized treatment protocols are intuitive and rational based on multiple clinical observations. With the 2-year CATT data demonstrating that PRN therapy results in significantly less VA gain, it is likely that most evidence-based treatment protocols will abandon the PRN approach. It is likely that the CATT data will convert more clinicians to switch to the prospectively untested “treat-and-extend” regimen or monthly therapy. In retrospective data, such treat and extend protocols significantly reduce the burden of care for patients and physicians, decrease the cost of care delivery and result in equivalent visual outcomes. The time is ripe for a large, prospective treat and extend protocol for exudative AMD management.

### **Rational for Year 3**

To determine if subjects who are dry and have been extended to a 12-week interval can maintain their dry macular status without continued ranibizumab injections.

To determine if subject who are dry on monthly dosing can maintain their dry macular status without continued ranibizumab injections.

To continue to attempt to extend and optimize treatment intervals for subjects with less than 12-week intervals between injections in the TREX arm.

## **3.4 OUTCOME MEASURES**

### **3.4.1 Primary Outcome Measure**

- Mean change in ETDRS visual acuity from baseline to weeks 24-28, baseline to weeks 48-56, baseline to weeks 72-82, baseline to week 104, baseline to weeks 128-132 and baseline to week 156.

### **3.4.2 Secondary Outcome Measures**

- Incidence and severity of adverse events (ocular and non-ocular).
- Total number of intravitreal injections required from baseline through weeks 48-57 (week closest to week 52), baseline through week 104 and baseline through week 156.
- Total number of office visits and imaging studies performed from baseline through weeks 24-28 (week closest to week 26), baseline through weeks 48-56 (week closest to week 52), baseline through weeks 72-82 (week closest to week 78), baseline through week 104, baseline through weeks 128-132 (week closest to week 132) and baseline through week 156.
- Percentage of subjects with persistent active exudation on SD-OCT from baseline through weeks 48-57 (week closest to week 52), baseline through week 104 and baseline through week 156.

- Percentage of subjects with persistent leakage on fluorescein angiography from baseline through weeks 24-28, baseline to weeks 48-56, baseline to weeks 72-82, baseline to week 104, baseline to weeks 128-132 and baseline to week 156.
- CNVM lesion size at baseline, compared to baseline to weeks 24-28, baseline to weeks 48-56, baseline to weeks 72-82, baseline to week 104, baseline to weeks 128-132 and baseline to week 156, as determined by fluorescein angiography.
- Mean change in central foveal thickness by SD-OCT from baseline to weeks 48-57, baseline to week 104 and baseline to week 156.
- Mean change in BCVA by ETDRS letter score from baseline through weeks 24-28, baseline through weeks 48-56, baseline through weeks 72-82, baseline to week 104, baseline through weeks 128-132 and baseline to week 156.

### Endpoint Visits:

Few completed prospective trials have employed a treat and extend protocol. Therefore, there is little data regarding optimal endpoint usage. These endpoints will allow comparison of data from each cohort.

1. **Floating Endpoints** (also known as the Biological Endpoints): Analyses will be performed between weeks 24-28, between weeks 48-57, between weeks 72-82, week 104, between weeks 128-132 and week 156 (range to be determined by timing of last injection). If more than one possible endpoint exists, the time point closest to week 26, week 52, week 78, week 104, week 130 or week 156 will be used. This will be applied to both Cohort A and B, but likely to be most important for Cohort B. All endpoints are measured 4 weeks following the last injection.
2. **Hard Endpoints**: analyses will be performed at week 52 (day 365 $\pm$  7 days), week 104 (day 730  $\pm$  7 days) and week 156 (day 1095)

### 3.5 SAFETY PLAN

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

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

To minimize the risks of intraocular injections, all injections will be performed employing surgical sterile techniques as described in Appendix B. Intraocular pressure will be measured before and 30 minutes ( $\pm$  15 minutes) after each ranibizumab injection. Any subject who develops significantly raised intraocular pressure ( $\geq$  30 mmHg) at any time during the study should be monitored according to the physician's clinical judgment and may undergo additional measurements of intraocular pressure beyond those specified in the protocol

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 or designated sub investigators on an ongoing basis.

### **3.6 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**

60 subjects from approximately 4 sites in the United States will be enrolled. Eligible subjects who have provided informed consent will be screened for eligibility before the initiation of any study procedures. Screening evaluations may be performed at any time within the 14 days preceding Day 0. Subjects must have wet macular degeneration secondary to age, with no prior treatment; with disease activity seen on SD-OCT. Subjects can only have one eye in the study, if both eyes are eligible to be in the trial the investigator will determine which eye will be in the study (study eye). Genentech will supply drug for the non-study eye (fellow eye) if needed. Subjects will be randomized in a 1:2 ratio so that:

- 20 subjects will be randomized to the monthly arm (Cohort A)
- 40 subjects will be randomized to the TREX arm (Cohort B)

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

#### **4.1.2 Inclusion Criteria**

Subjects will be eligible if the following criteria are met:

- Ability to provide written informed consent and comply with study assessments for the full duration of the study
- Age  $\geq$  50 years

#### 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

- Any CNVM lesion (Occult, Minimally Classic or Classic) (i.e., leakage on fluorescein angiography or subretinal, intraretinal activity on SD-OCT) secondary to age-related macular degeneration.
- Best corrected visual acuity in the study eye, using ETDRS testing, between 20/32 and 20/400 (Snellen equivalent), inclusive.
- Only one eye will be enrolled in the Study. If both eyes are eligible study investigator will select the eye for entry.
- The total area of subretinal hemorrhage and fibrosis must comprise less than 50% of the total lesion.
- 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 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 vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in the study eye

- Prior treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy (TTT) in the study eye at a fluence equal to 100%, any fluence lower than 100% is permitted.
- Any Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs including ranibizumab, or device implantation) in the study eye.

#### CNV Lesion Characteristics

- Subretinal hemorrhage in the study eye that involves the center of the fovea, if the size of the hemorrhage is either > 50% of the total area of the lesion or > 1 disc area (2.54 mm<sup>2</sup>) in size
- Subfoveal fibrosis or atrophy in the study eye
- CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia

#### Concurrent Ocular Conditions

- Retinal pigment epithelial tear involving the fovea in the study eye
- Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) 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 or absence of the posterior capsule in the study eye
- Intraocular surgery (including cataract surgery) in the study eye within 2 months preceding Day 0
- Uncontrolled glaucoma in the study eye (defined as IOP ≥ 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

- 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**

Subjects will receive open-label IVT of 0.5 mg ranibizumab. Subjects will be randomized into a 1:2 ratio that will occur at Day 0.

- Cohort A – Subjects will receive monthly treatment of 0.5 mg IVT ranibizumab for 100 weeks. Starting at week 104 subjects will receive PRN IVT ranibizumab for another 56 weeks (total of 156 weeks)
- Cohort B – Subjects will receive 0.5mg IVT ranibizumab for 3 a minimum of consecutive visits (visit 2, 4 & 5) followed by a treat and extend protocol in which follow-up intervals are increased when there is no clinical and SD-OCT evidence of disease activity by 2-week intervals. Starting at week 104, if a subject has achieve the 12 week interval they will switch to monthly visits with PRN IVT ranibizumab through week 156. If a subject has not achieved a dry macula they will continue the treat and extend protocol until the 12 week interval is met and then switch to monthly visits with PRN IVT ranibizumab.

## **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 10-mg/mL ranibizumab aqueous solution with 10 mM histidine HCl, 10%,  $\alpha$ -trehalose dihydrate, and 0.01% polysorbate 20, pH 5.5. This results in the delivery of a 0.5 mg dose of ranibizumab. Each vial contains no preservative and is suitable for single use only.

Further details and molecule characterization are included in the Investigator Brochure.

#### **4.3.2 Dosage, Administration, and Storage**

##### **a. Dosage**

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

##### **b. Administration**

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

##### **c. Storage**

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

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

#### **4.4 CONCOMITANT AND EXCLUDED THERAPIES**

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

#### **4.5 STUDY ASSESSMENTS**

##### **4.5.1 Assessments during the Treatment Period**

\* Refer to Appendix A for a complete overview of study procedures

- Obtain informed consent prior to study procedures being performed at screening visit
- Obtain demographics
- Concomitant Medications reviewed at every visit
- Adverse Events reviewed at every visit

##### Vital Signs (All Study Visits)

- Vital signs will include measurements of pulse and systolic and diastolic blood pressure, while subject 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. (See Appendix F)
- IOP measurement of both eyes will be measured pre-dilation at every visit. IOP will be measured post intravitreal injection 30 min ( $\pm$  15 min) in the study eye. The method used for a subject must remain consistent throughout study.
- Slit lamp examination-Subject's anterior eye structure and ocular adnexa will be examined at each study visit using a slit lamp by the investigator.
- Indirect Ophthalmoscopy the subject's posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre dose by the investigator
- Subjects will receive 0.5 mg intravitreal injection of ranibizumab per treatment schedule
- Telephone Safety Check 3 days ( $\pm$  1 day) post injection (after first injection only)

### Ocular Imaging

- Fundus Photography (FP) and Fluorescein Angiography (FA)- The anatomical state of the retinal vasculature of the study eye will be evaluated by fundoscopic examination, FP and FA. As well, as a measurement of the CNVM size performed at Screen, between weeks 24-28, 48-57, between weeks 72-82, between weeks 104, between weeks 124-128 and week 156.
- Optical Coherence Tomography (All Study Visits) – Ocular morphology will be evaluated using the Heidelberg Spectralis 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.
- Auto Fluorescence (AF) (All Study Visits) – Ocular morphology will be evaluated using the Heidelberg Spectralis on the study eye. All AF images will be captured using the most current software. All AF's will be electronically archived at the site as part of the source documentation

\*See Appendix E for Imaging Guidelines

### Other Testing (Performed at week 104, week 128 & week 156 or closest visit to each)

- Serum and/or plasma Samples

### Procedures performed at Endpoint Visits (if separate from a scheduled visit)

- Floating Endpoints (also known as the Biological Endpoints): ETDRS visual acuity, SD-OCT, AF, FP and FA
- Hard Endpoints: ETDRS visual acuity, SD-OCT and AF

#### **4.5.2 Early Termination Assessments**

Subjects who withdraw from the study prior to completion should return for an early termination evaluation 28 days ( $\pm$  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. The Retina Consultants of Houston or Charles C. Wykoff, PhD, 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**

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

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

#### **4.8 STATISTICAL METHODS**

##### **4.8.1 Analysis of the Conduct of the Study**

The analysis of data from week 52, week 104 and week 156 treatment period will be performed when all subjects have either completed the visit at week 52, week 104 and week 156 or discontinued early from the study.

The analysis of complete data (week 156) for the study will be performed when all subjects have either completed the visit at week 156 or discontinued early from the study, all data collected from the study are in the database, and the database is locked. Aggregate results of the week 52, week 104 and week 156 analysis, summarized by treatment group, may be reported to the public before completion of the study.

Descriptive summaries will include the mean, standard deviation, median, and range for continuous variables, counts and percentages for categorical variables.

Unless otherwise specified, all statistical tests are two sided. Detailed specifications of the statistical methods are described in the Statistical Analysis Plan.

#### **4.8.2 Safety Analyses**

Any adverse events, laboratory assessments, physical examinations, vital signs, ocular examinations and measurements from all 60 subjects will be utilized to summarize safety data for this study.

#### **4.8.3 Efficacy Analyses**

##### **Primary Outcome Measure**

The primary outcome measure for safety, tolerability and efficacy are:

- Mean change in ETDRS visual acuity from baseline to weeks 24-28, baseline to weeks 48-56, baseline to weeks 72-82, baseline to week 104, baseline to weeks 128-132 and baseline to week 156.

##### **Secondary Outcome Measures**

- Incidence and severity of adverse events (ocular and non-ocular).
- Total number of intravitreal injections required from baseline through weeks 48-57 (week closest to week 52), baseline through week 104 and baseline through week 156.
- Total number of office visits and imaging studies performed from baseline through weeks 24-28 (week closest to week 26), baseline through weeks 48-56 (week closest to week 52), baseline through weeks 72-82 (week closest to week 78), baseline through week 104, baseline through weeks 128-132 (week closest to week 132) and baseline through week 156.
- Percentage of subjects with persistent active exudation on SD-OCT from baseline through weeks 48-57 (week closest to week 52), baseline through week 104 and baseline through week 156.

- Percentage of subjects with persistent leakage on fluorescein angiography from baseline through weeks 24-28, baseline to weeks 48-56, baseline to weeks 72-82, baseline to week 104, baseline to weeks 128-132 and baseline to week 156.
- CNVM lesion size at baseline, compared to baseline to weeks 24-28, baseline to weeks 48-56, baseline to weeks 72-82, baseline to week 104, baseline to weeks 128-132 and baseline to week 156, as determined by fluorescein angiography.
- Mean change in central foveal thickness by SD-OCT from baseline to weeks 48-57, baseline to week 104 and baseline to week 156.
- Mean change in BCVA by ETDRS letter score from baseline through weeks 24-28, baseline through weeks 48-56, baseline through weeks 72-82, baseline to week 104, baseline through weeks 128-132 and baseline to week 156.

### **Endpoint Visits:**

Few completed prospective trials have employed a treat and extend protocol. Therefore, there is little data regarding optimal endpoint usage. These endpoints will allow comparison of data from each cohort.

1. **Floating Endpoints** (also known as the Biological Endpoints): Analyses will be performed between weeks 24-28, between weeks 48-57, between weeks 72-82, week 104, between weeks 128-132 and week 156 (range to be determined by timing of last injection). If more than one possible endpoint exists, the time point closest to week 26, week 52, week 78, week 104, week 130 or week 156 will be used. This will be applied to both Cohort A and B, but likely to be most important for Cohort B. All endpoints are measured 4 weeks following the last injection.
2. **Hard Endpoints:** analyses will be performed at week 52 (day 365 $\pm$  7 days), week 104 (day 730  $\pm$  7 days) and week 156 (day 1095)

#### **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.

#### **4.8.6 PK/PD Analyses**

Optional Serum and/or plasma samples collected for PK/PD analysis will be analyzed for biomarkers including but not limited to isoforms of VEGF and ranibizumab. The samples will be stored at either Retina Consultants of Houston or Genentech after the testing. Residual serum and plasma remaining once the primary analyses are completed may be used for

further exploratory analyses of VEGF and other systemic biomarkers related to angiogenesis, atherosclerosis, and inflammation.

#### **4.9 DATA QUALITY ASSURANCE**

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

### **5. ASSESSMENT OF SAFETY**

#### **Specification of Safety Variables**

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

#### **5.1 ADVERSE EVENTS**

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution. AE's will be recorded from screen through week 156.

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

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

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

#### **5.2 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES**

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

##### **5.2.1 Adverse Event Reporting Period**

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment or "initiation of any non-standard of care study procedures" and ends 30 days

following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

### **5.2.2 Assessment of Adverse Events**

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

## **5.3 EVALUATIONS**

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

## **5.4 VITAL SIGNS**

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

## **5.5 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS**

### **5.5.1 Eliciting Adverse Events**

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

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

### **5.5.2 Specific Instructions for Recording Adverse Events**

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

#### **5.5.2.1 Diagnosis vs. Signs and Symptoms**

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

### **5.5.2.2 Deaths**

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

### **5.5.2.3 Preexisting Medical Conditions**

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

### **5.5.2.4 Hospitalizations for Medical or Surgical Procedures**

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

Hospitalizations for the following reasons do not require reporting:

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

### **5.5.2.5 Pregnancy**

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

#### 5.5.2.6 Post-Study Adverse Events

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

#### 5.5.2.7 Reconciliation

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

#### 5.5.2.8 AEs of Special Interest (AESIs)

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

The ranibizumab Events of Special Interest are:

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

#### 5.5.2.9 Evaluation of Causality

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

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

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

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

#### 5.5.2.10 Evaluation of Severity

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

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

### 5.6 SERIOUS ADVERSE EVENTS

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

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

### **5.6.1 Criteria for Serious Sight-Threatening Ocular Adverse Events :**

- Adverse event causes a decrease in BCVA of > 30 letters (compared with the most recent assessment of BCVA) lasting > 1 hour
- Adverse event causes a decrease in VA to the level of light perception or worse
- Adverse event requires surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight
- Adverse event is associated with severe intraocular inflammation (ie, 4+ anterior chamber cell/flare or 4+ vitritis)
- In the opinion of the investigator, AE may require medical intervention to prevent permanent loss of sight

### **5.6.2 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 0.5 mg ranibizumab and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the 0.5 mg ranibizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

Additional Reporting Requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with the 0.5 mg ranibizumab and 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.

### **5.6.3 MedWatch 3500A Reporting Guidelines**

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

- Protocol description (and number, if assigned)

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

#### **5.6.4 Follow-up Information**

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

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

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request. MedWatch 3500A (Mandatory Reporting) form is available at <http://www.fda.gov/medwatch/getforms.html>

#### **5.6.5 Additional Reporting Requirements for IND Holders**

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

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

##### 7 Calendar Day Telephone or Fax Report

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of 0.5 mg ranibizumab. An unexpected adverse event is one that is not already described in the 0.5 mg ranibizumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

### 15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of 0.5 mg ranibizumab. An unexpected adverse event is one that is not already described in the 0.5 mg ranibizumab investigator brochure.

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

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

### FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

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

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

### **And to the Site IRB:**

Sterling Institutional Review Board  
6300 Powers Ferry Road  
Suite 600-351  
Atlanta, Georgia 30339

Toll-Free: 888-636-1062

Phone: 770-690-9491

Fax: 770-690-9492

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

Tel: (888) 835-2555

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

### IND Annual Reports

#### **Copies to Genentech:**

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

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

**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.

## 5.6.6 SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	
Follow-up Report Date	

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 Retina Consultants of Houston 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 Retina Consultants of Houston, 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](http://www.clinicaltrials.gov)) (as applicable)
- Investigator Brochure Signature Receipt

### **6.2 STUDY COMPLETION**

The following data and materials are required by Retina Consultants of Houston 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 Retina Consultants of Houston 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 Retina Consultants of Houston (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

## **6.5 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.

## **6.6 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.

## **6.7 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.

## **6.8 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. References:

Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *The New England journal of medicine*. 2006;355(14):1432-1444.

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Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *American journal of ophthalmology*. 2008;145(2):239-248.

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Oubraham H, Cohen SY, Samimi S, et al. Inject and extend dosing versus dosing as needed: a comparative retrospective study of ranibizumab in exudative age-related macular degeneration. *Retina*. 2011;31(1):26-30.

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APPENDIX Year 1 T-REX/ Treat and Extend for Wet AMD/(Monthly)Control Arm/Cohort 1

Week (±7 days)	Screen	Day	Day 7	4	8	12	16	20	24	28	32	36	40	44	48
Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit
Sign IFC	X														
Medical/Oph HX	X														
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interval History (AE & Con Meds)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect/Slit Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP (Pre & Post Injection)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Auto Fluorescence	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus Photo/ FA	X								X						
CNVM Measurement	X								X						
Study Drug Injection		X		X	X	X	X	X	X	X	X	X	X	X	X
Telephone Safety check (±3 days)		X													

\*\*\*\* Additional measurements will need to be scheduled 4 weeks post injection within the "quarterly report" windows defined below. In the event that two possible additional sessions (4 weeks post injection) can be scheduled within a quarterly window, schedule the session, which falls closest to month 6 (week 24), month 12 (week 52), month 18 (week 78), month 24 (week 104), month 30 (week 128) or month 36 (week 156) mark.

Ye T-REX/ Treat and Extend for Wet AMD/(Monthly) Control Arm/Cohort 1 (cont'd)

Week (±7 days)	52	56	60	64	68	72	76	80	84	88	92	96	100	104
Visit	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	Visit 26	Visit 27	Visit 28	Visit 29
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Interval History (AE & Con Meds)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect/Slit Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP (Pre & Post Injection)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Auto Fluorescence	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FP/ FA	X						X							X
CNVM	X						X							X
Measurement														
Study Drug Injection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum and/or Plasma Blood Draw														X

1. Injection administered on a PRN basis, if meets re-treatment criteria 2. Optional

Year 3 T-REX/PRN Treatment Schedule

Week (±7 days)	108	112	116	120	124	128	132	136	140	144	148	152	156
Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit
Vital Signs	30 X	31 X	32 X	33 X	34 X	35 X	36 X	37 X	38 X	39 X	40 X	41 X	42 X
Interval History (AE & Con Meds)	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect/Slit Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP (Pre & Post Injection)	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X
Auto Fluorescence	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus Photo/ FA						X							X
CNVN Measurement						X							X
Study Drug Injection	X <sup>1</sup>												
Serum and/or plasma						X <sup>2</sup>							X <sup>2</sup>

1. Injection administered on a PRN basis, if meets re-treatment criteria      2. Optional

T-REX/Treat and Extend Arm/Cohort 2

		Week 12-156					
Week (±7 days)	Screen	Day0	Day7	4	8		
Visit	Visit	1	2	3	4	5	
Sign IFC	X						
Medical/Oph HX	X						
Vital Signs	X	X	X	X	X	X	
Interval History (AE & Con Meds)	X	X	X	X	X	X	
Indirect/Slit Lamp Exam	X	X	X	X	X	X	
IOP (Pre & Post Injection)	X	X	X	X	X	X	
Visual Acuity (ETDRS)	X	X	X	X	X	X	
SD-OCT	X	X	X	X	X	X	
Auto	X	X	X	X	X	X	
Fluorescence FP/FA	X						
CNVM Measurement	X						
Study Drug Injection <sup>2</sup>		X			X	X	
Plasma and/or Serum Sample <sup>1,3</sup>							

- Cohort 2 will receive 3 mandatory 0.5mg ranibizumab injections (Day 0, week 4, & week 8)
- Interval will remain at 4 weeks until there are no signs of exudative disease on SD-OCT or clinical examination
- Once a dry macula is achieved meaning there are no signs of exudative disease on SD-OCT or clinical examination the subject will start the Treat and Extend protocol, interval between injections is increased by 2-week intervals, starting at visit 6.
  - o Treatment Interval will not exceed > 12 weeks.
- If recurrent exudative disease is detected at any visit, after extension has been met, the interval between injections will decrease by 2 weeks (compared to the previous interval) until a "dry" macula is again established or subject is back at the 4-week interval.
  - o Once a dry macula is again achieved the interval between visits will extend by 1-week intervals.
  - o If subject again shows signs of recurrent exudative disease, interval will be by 1 week until dry or subject is back at 4 week interval
  - o Once macula is again dry, treatment interval remains at the same interval for 1 more treatment, after which the treatment interval will be increased by 1-week intervals if the macula remains dry.
    - If patient shows signs of exudative disease 3 times at a certain interval, interval will be decreased by 1 week intervals until the macula is dry AND then remain at this reduced interval for 3 sessions then re-start the treat and extend protocol (meaning extend by 2 week intervals at every visit a dry macula is achieved.
- **Endpoint Measurements:** Additional visits will be scheduled 4 weeks post injection within the "quarterly report" windows defined below. In the event that two possible additional sessions (4 weeks post injection) can be scheduled within a quarterly window, schedule the session which falls closest to the 26 week, 52 week, 78 week, 104 week, 128 week and 156 week marks; if the two sessions are equally spaced around an endpoint, use the earlier. Refer to protocol for visit windows for floating endpoint visits. BCVA, SD-OCT, AF and FA/FP will be performed at the floating endpoint visits.
  - Hard-endpoints will be additional visits at week 52, week 104, and week 156 (± 7 days). BCVA, AF and SD-OCT will be performed at the hard end point visits.

1. Performed at week 104, week 128 & week 156 2. Study drug injection not administered at week 156 3. Optional

## **APPENDIX B- Pre-administration, Administration, and Post-administration**

### **Procedures for Intravitreal Injections**

The following procedures will be implemented to minimize the risk of potential adverse events associated with intravitreal injections (e.g., endophthalmitis). Staff will observe aseptic technique involved in the injection assembly, anesthetic preparation, 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. Supplies include 10% povidone iodine swabs, gloves, 4x4 sterile pads, pack of sterile cotton-tipped applicators, eyelid speculum, 0.5% proparacaine hydrochloride, 5% povidone iodine ophthalmic solution, 2% lidocaine for subconjunctival injection (if needed), ophthalmic antimicrobial solution (e.g., trimethoprim-polymyxin B ophthalmic solution, ofloxacin ophthalmic solution, ophthalmic gatifloxacin solution, ophthalmic moxifloxaacin solution, etc) and injection supplies.

### **Pre-Administration**

- Instill topical anesthetic.
- Instill an ophthalmic antibiotic.
- Subconjunctival anesthesia is optional per investigator's discretion: injection 0.5 mL of 2% lidocaine without epinephrine at the injection site.
- Disinfect the periocular skin and eyelid of the study eye. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Make certain that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.
- At investigator's discretion, different antiseptic may be used may be used for periocular preparation.
- The Investigator will glove and place a speculum underneath the eyelids of the study eye.
- Instill 5% povidone iodine ophthalmic solution in the study eye, making sure the drops cover the planned injection site on the conjunctiva.
- Wait a minimum of 30 seconds before intravitreal injection.
- Instruct subject to directly gaze away from syringe prior to injection.

### **Administration of Intravitreal Injection**

- Using aseptic technique, all of the ranibizumab vial contents are withdrawn through a 5µm, 19g filter needle attached to a 1cc tuberculin syringe.
- The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection.
- Replace the filter needle with a sterile 30g, ½" needle for the injection (or smaller).
- 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 determining subject's ability to see from the study eye.
- Measure intraocular pressure (IOP) 30 minutes ( $\pm$  15 minutes) after the injection.
- Subject will continue to be monitored until IOP is  $\leq$ 30 mmHg.

\*\*\*If a sites injection procedure differs from what is described above, site SOP or manual of procedures can be submitted 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 previous 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, Retina Consultants of Houston believes there is a reasonable possibility of a cause-and-effect relationship between administration of \_\_\_\_\_ (insert study drug name) and the occurrence of \_\_\_\_\_ (insert AE).

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

Or

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

Explain if warranted. Do not speculate.

Or

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

Explain if warranted. Do not speculate.

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

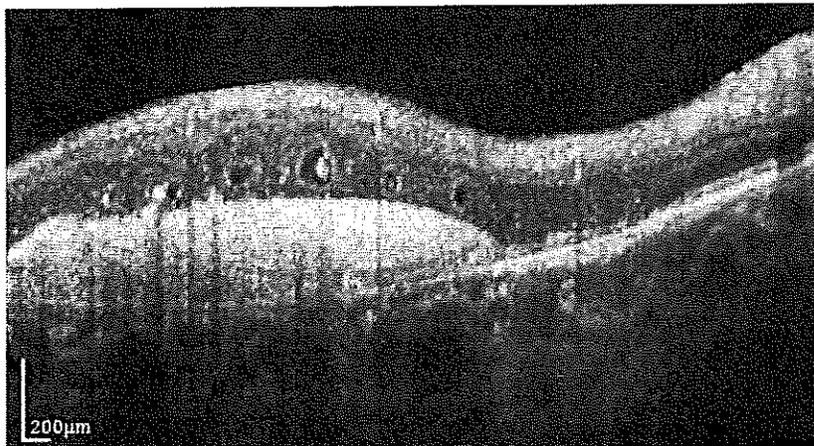
APPENDIX D

TREX Associated Figures

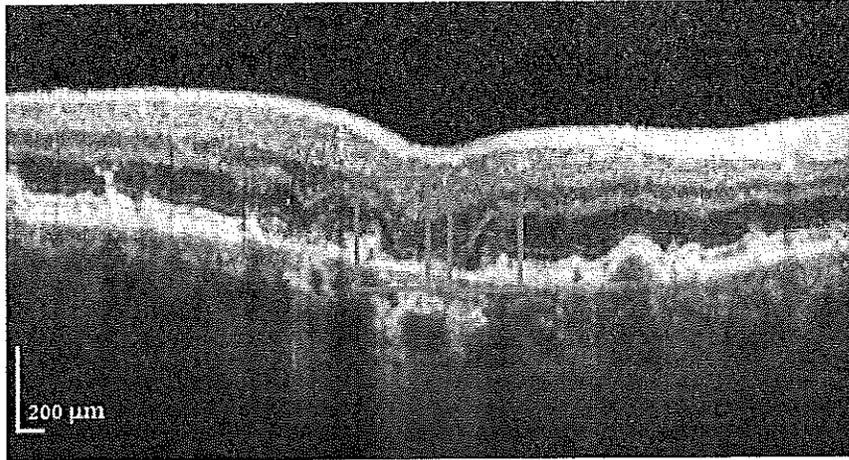
SD-OCT findings that are not evidence of active wet AMD



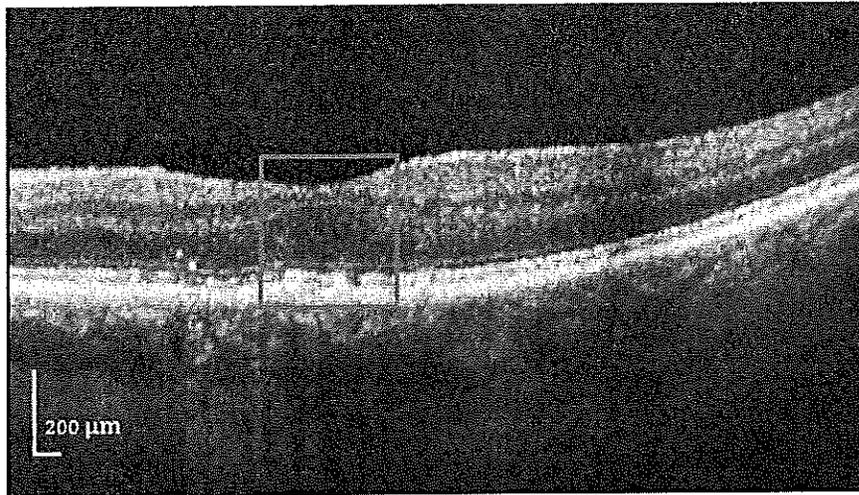
**Figure 1: Chronic cystic spaces consistent with ORT  
(Outer-retinal tubulation)**



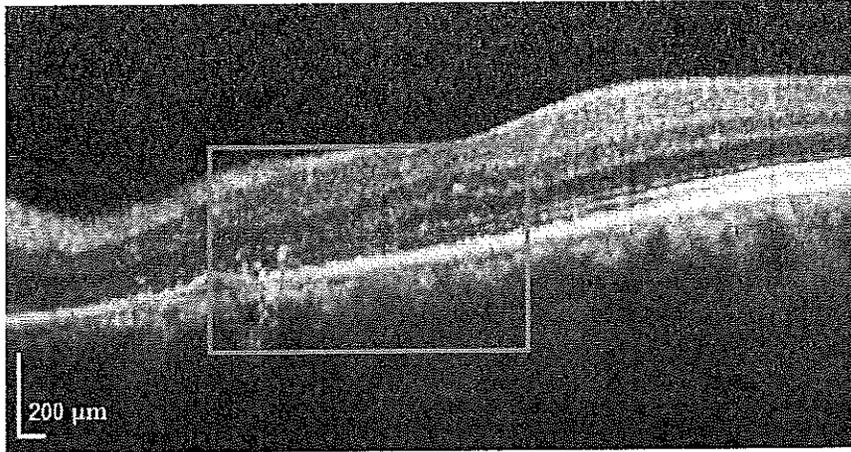
**Figure 1: Chronic cystic spaces consistent with ORT  
(Outer-retinal tubulation)**



**Figure 2: Chronic small cysts associated with atrophic area. Small hypo-dense areas seen with SDOCT overlying areas of outer-retinal atrophy are often not evidence of exudative disease activity.**



**Figure 3: Hypo-dense areas that are not consistent with cysts**



**Figure 4: Hypo-dense areas that are not consistent with cysts**

## APPENDIX E

### Imaging Guidelines

#### OCT

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

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

Scans should be centered on the fovea.

After initial scan set as a reference and all subsequent SD-OCT's done to reference.

#### Auto Fluorescence

1 pair of each eye OU

#### Color Fundus Photo Photography

Fundus Photos of both eyes should be taken in stereo pairs of macula and optic nerve:

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

#### Fluorescein Angiography

- 1) Stereo red free of the macula
- 2) Take on control picture prior to injection. Fluorescein angiography is performed in the usual manor (intravenous injection of 2.5 ml of 5% or 5 ml fluorescein solution). Inject fluorescein as rapidly as possible using a 21 or 23 gauge infusion set. The study eye will be the transit eye.
- 3) Take a picture of the study eye as soon as the fluorescein dye has been completely injected
- 4) Take 6-8 photos during the dye transit phase
- 5) At one minute take 1 stereo pair of the macula OU
- 6) At 2 minutes take 1 stereo pair of the macula and optic nerve OU
- 7) At 5 minutes take 1 stereo pair of the macula

## Appendix F

### BEST-CORRECTED VISUAL ACUITY PROTOCOL

#### 1. Visual Acuity Equipment and Facilities

##### 1.1 Introduction

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

The charts and boxes could be provided by:

**Optelec featuring Lighthouse Products**

3030 Enterprise Court, Suite C

Vista, CA 92081

Telephone: 800-826-4200

Fax: 800-368-4111

**Precision Vision**

944 First Street

La Salle, IL 61301, USA

Telephone: 800-772-9211

Fax: 815-223-2224

**Sussex Vision Intl. Ltd.**

A2, Dominion Way

Rustington

West Sussex BN16 3HQ, United Kingdom

Telephone: 01903 851951

Fax: 01903 767732

[www.sussexvision.co.uk](http://www.sussexvision.co.uk)

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

## 1.2 Visual acuity charts

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

## 1.3 Visual acuity box

The dimensions of the light box are 24 and  $\frac{3}{4}$  inches (62.9 cm) by 25 and  $\frac{3}{4}$  inches (65.4 cm) by 7 inches (17.8 cm). The box can be mounted on a wall, on a countertop, or on a cylindrical stand manufactured by Optelec featuring Lighthouse Low Vision Products or Precision Vision. The stand is mounted on a five-pronged wheelbase, with each prong about 14 inches (35.6 cm) long. Two of the five wheels are lockable. When the box is mounted on the stand, its height can be varied.

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

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

## 1.4 Illumination

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

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

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

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

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

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

#### 1.5 4 and 1 meter visual acuity lanes

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

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

1. Wall-mounted box: In addition to the 4 meter lane, 7 inches (17.8 cm) must be allowed for the depth of the box plus space for the participant to sit or stand.
2. Stand-mounted box: In addition to the 4 meter lane, 13 inches (33 cm) must be allowed for two of the stand's casters to touch the rear wall (or a line marked on the floor when there is no wall) plus space for the participant to sit or stand.

## 1.6 Marking the distance

### 4 meters

1. If the chair and visual acuity box are permanently affixed, distance measurements need to be made only once and the wall should be clearly marked in order to properly align each individual study subject while being tested.
2. If the box is mounted on the wall but the participant's chair is not permanently affixed, the 4 meter distance of the participant's eye from the chart must be marked clearly and permanently both on the floor and the wall closest to the subject's chair.
3. If the box is mounted on a movable stand, the 4 meter distance must be marked clearly and permanently on the floor and on the wall. The location and orientation of the box must be rechecked each time a new chart is put in place or the box is touched. Two of the five casters should touch the wall or face the rear orientation.

### 1 meter

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

## 2. Refraction Technique

### 2.1 Introduction

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

### 2.2 Beginning approximate refraction

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

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

1. If the participant's uncorrected visual acuity is 20/200 (LogMAR 1.0) or better and the participant does not have glasses for distance vision, the beginning approximate refraction is no lens correction (plano).
2. If the participant's uncorrected visual acuity is less than 20/200 (LogMAR 1.0) in either eye with the participant's present distance glasses (or without correction, if the participant does not have glasses), retinoscopy should be performed by an examiner proficient in the procedure. An acceptable alternative is to conduct an arbitrary trial with any lenses to

bring acuity to 20/200 (LogMAR 1.0) or better. Another is to use an automated refractor. The lens corrections obtained are used as the beginning approximate refraction for determining best corrected visual acuity (Section 3).

3. If the participant's visual acuity is 20/200 (LogMAR 1.0) or better with the participant's present distance glasses, the glasses are measured with a lensometer, and these measurements are used as the beginning approximate refraction.

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

### 2.3 Subjective refraction

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

### 2.4 Determination of spherical refraction

Refer to the following chart when selecting testing lens powers:

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

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

1. If vision is improved or there is no change, the sphere in the trial frame is replaced with one that is one-half diopter more plus. The +0.50 sphere is again held in front of the right eye, and the participant is asked again if the vision is "better," "worse," or "no different." This process of increasing the plus sphere in the trial frame is repeated until the participant states that the +0.50 sphere held in front of the trial frame makes the vision worse. When the participant responds that the vision is made "worse," the lens should be left in place for 10 to 15 seconds in an attempt to evaluate

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

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

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

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

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

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

improve vision, again offer a +0.50 sphere to determine if more plus would be accepted. Always end up offering plus power.

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

## 2.5 Determination of cylindrical refraction

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

### 1. Cylinder axis determination:

If the beginning approximate refraction contains a cylinder correction, changes in cylindrical axis are tested by adding a 0.25, 0.50, or 1.00 diopter cross cylinder (refer to chart under Section 2.4), first with the positive axis 45 degrees to one side of the cylinder axis, and then with the positive axis 45 degrees to the opposite side of the cylinder axis. Since neither position may produce a clear image, the participant is encouraged to select the position producing the least blur while fixing on a single round letter on the line above the lowest line on the chart he or she is able to read when the cross cylinder is not held up before the trial frame.

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

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

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

## 2. Cylinder Power Determination:

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

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

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

If the beginning refraction is a “pure” sphere, the presence of astigmatism is tested by arbitrarily placing a +0.25 cylinder at 180 degrees in the trial frame, after having determined the highest plus or least minus sphere producing minimal blurring of vision, as described above. The refraction is then continued by using the cross cylinder to test for cylinder axis and then cylinder power using the technique outlined above. If at any time the

preference with the cross cylinder indicates that cylinder power should be removed entirely, the 0.25 cylinder should be rotated 90 degrees from its original position, and the power should be tested again. At this point, if the participant prefers additional power, it should be added. If, on the other hand, the participant prefers to remove the +0.25, it should be removed and the final refraction is then purely spherical. An example of the procedure follows:

Beginning refraction: -2.50 + 0.25 axis 90 degrees. Use of the cross cylinder to check cylinder axis indicates that the participant prefers the 90 degree axis. If, on using the cross cylinder to check cylinder power, the participant wants the 0.25 cylinder removed, rotate the cylinder to 180 degrees and test for cylinder power again. If additional power is preferred, it should be added, remembering to adjust sphere as needed. If the preference with the cylinder at 180 degrees is to remove the 0.25 cylinder, this should be done, and the resulting refraction is -2.50 sphere.

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

## 2.6 Refining final spherical power

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

This refraction protocol can be summarized as follows: First, having eliminated any possible accommodation with plus spheres, the spherical equivalent power is placed on the retina. Then, the cylinder power and cylinder axis are assessed. This process of checking sphere, cylinder axis, and cylinder power is repeated until there are no changes that result in an increased number of letters being read. Ideally, at the end of the refraction, the sphere is checked, and the participant neither tolerates increased plus nor improves with increased minus spheres. Then, the axis is checked, and no change in axis is indicated. Finally, the cylindrical power is

checked, and no change in this is indicated. At this point, the refraction is completed. Sometimes this endpoint cannot be reached because there are an unending number of small corrections at each repetition of the process. When it becomes clear that these small changes are not resulting in an increased number of letters read correctly, the examiner can terminate the refraction.

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

### 2.7 Adjustment for non-standardized test conditions

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

### 2.8 Refraction for participant with poor visual acuity

If it is not possible to perform refraction at the 4 meter distance because of decreased vision or impaired mental aptitude, which prohibits the participant from correctly reading 4 or more letters, the refraction should be attempted at 1 meter. Before attempting the 1 meter refraction, +0.75 sphere must be added to the last 4 meter refraction obtained (during follow-up this is the previous refraction result obtained from the refraction data sheet), which is to be used as the starting refracting. If the subjective refraction can be successfully performed at 1 meter, a +0.75 sphere should be subtracted from the final 1 meter refraction to make the

correction appropriate for the 4 meter distance. The refraction procedure at 1 meter is the same as the procedure for 4 meters. However, if the participant is unable to discern changes in letter clarity using the lens increments outlined for the 4 meter refraction, larger increments of lens power should be used. When checking the sphere,  $\pm 1.00$  diopter should be tested. If the participant still cannot perceive any difference in clarity, changes up to  $\pm 3.00$  diopters can be attempted. Cylindrical refraction can be assessed with the 0.50 or 1.00 diopter Jackson cross cylinder rather than the 0.25 diopter cross cylinder. When changing the sphere power, use 1.00 diopter increments for adding plus, and 0.50 diopter increments for adding minus. When changing cylinder power, add or subtract cylinder power in 0.50 diopter increments.

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

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

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

## 2.9 Special situations

Occasionally, one will need to perform refraction and visual acuity on participants with medical or other conditions that make the routine testing difficult, such as

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

### 3. Testing Best Corrected Visual Acuity

#### 3.1 4 meter test

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

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

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

The participant should be asked to read slowly (at a rate not faster than about one letter per second) in order to achieve the best identification of each letter and to not

proceed until the participant has given a definite response. It may be useful for the examiner to demonstrate the letter-a-second pace by reciting "A, B, C, . . ." If, at any point, the participant reads quickly, he or she should be asked to stop and read slowly. If the participant loses his or her place in reading or the examiner loses his or her place (possibly because the letter are read too quickly), the examiner should ask the participant to go back to where the place was lost. Examiners should never point to the chart or to specific letters on the chart or read any of the letters during the test except for those situations as outlined in Section 2.7.

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

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

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

### 3.2 1 meter test

Eyes reading 19 or fewer letters correctly at 4 meters should be tested at 1 meter. If the trial frame is to be removed when changing the test distance from 4 meters to 1

meter, the testing chart (Chart 1 or 2) should first be removed from view to prevent the participant from reading the chart with the fellow eye.

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

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

### 3.3 Scoring best corrected visual acuity

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

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

If the participant reads 3 or fewer letters on the 20/800 line at 1 meter, visual acuity is assessed by counting fingers. During this test the examiner holds his or her fingers before the participant's eye good light and the vision is recorded as the

furthest distance at which the fingers can be counted. For example, if the participant can accurately count the number of fingers the examiner is holding up from 1 meter (approximately 3 feet) away, this is recorded as counting fingers at 1 meter (approximately 3 feet) on the Visual Acuity Worksheet Form. If the participant cannot distinguish fingers, the examiner should wave a hand in front of the participant's eye. If movements of the hand are perceived by the participants, then the vision is recorded as HM or hand movements.

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

#### **4. Staff Certification**

##### **4.1 Introduction**

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

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

- Spherical Equivalency
- Plus and Minus Spheres and Cylinders

- Hyperopia, Myopia, and Astigmatism
- "Push Plus" Refraction Principles

#### 4.2 Activities Requiring Certification

Training and certification are required for the following activities:

- ETDRS Refraction
- ETDRS Visual Acuity

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

#### 4.3 Forms of Valid Certification

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

#### 4.4 Study Facilities

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