PROTOCOL

STUDY TITLE:	*Treatment of Polypoidal Choroidal Vasculopathy with High Dose Ranibizumab (Lucentis):A Phase I Safety Study*
STUDY NUBMER	FVF4916s
STUDY DRUG	Recombinant humanized anti-VEGF monoclonal antibody fragment (rhuFab V2 [ranibizumab] {Lucentis})
SPONSOR	*Southeast Retina Center, P.C.* *3685 Wheeler Rd.* *Augusta, GA 30909*
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DATE FINAL:	15 November 2010

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1. BACKGROUND

1.1 PATHOPHYSIOLOGY

Polypoidal choroidal vasculopathy (PCV) is a type of choroidal neovascularization (CNV) that has occult characteristics on fluorescein angiography but demonstrates saccular dilations and polypoidal interconnecting vascular channels on indocyanine green angiography. PCV results in serosanguinous pigment epithelial detachments (PED) and neurosensory retinal detachments secondary to leakage and bleeding from the choroidal vascular lesions. PCV is a distinct clinical syndrome and the aneurysmal dilatations may be visible clinically as reddish-orange. PCV was originally recognized as a "uveal bleeding syndrome" often presenting with multiple recurrent hemorrhagic PED's in middle-aged, pigmented females. With time and recognition, a broader concept of PCV has occurred, including a broad range of ages, races including a propensity for Asians as well as African Americans, and both sexes (Yannuzzi 1997). While debated, the pathogenesis of the vascular abnormality in PCV has been proposed to be a likely variant of CNV (Uyama 1999), although others propose PCV as inner choroidal vessel abnormalities that are distinct from CNV (Yuzawa 2005). Within the expanding spectrum of PCV, there is some overlap in elderly patients initially classified as age-related macular degeneration (AMD). PCV may be differentiated from AMD in that PCV is more commonly observed in the peripapillary region, without associated drusen, and in non-white patients (Yannuzzi 1999). While the natural course of PCV is somewhat more favorable than AMD-associated CNV, active polypoidal lesions often cause subfoveal hemorrhagic PED's, subretinal fluid/exudates and fibrosis resulting in visual loss.

The stimuli that prod are unknown. However, there is evidence suggesting that angiogenic factors, such as vascular endothelial growth factor (VEGF), play a role in the pathogenesis of AMD-related CNV and in all forms of ocular neovascularization (see section 1.3). Systemic hypertension is associated with PCV.

1.2 TREATMENT OF PCV

Observation for asymptomatic, non-exudative PCV is recommended. The efficacy of any treatment modality for active, exudative PCV has not been established as large controlled trials have not been performed. Anecdotal evidence in case series indicates that PCV may respond to thermal laser (often ICG-guided) photocoagulation (Uyama 1999, Yannuzzi 1990, Nishijima 2004) or photodynamic therapy (PDT) with Visudyne (Spaide 2002, Chan 2004, Silva 2005, Nazimul 2005). Other therapies for CNV such as periocular steroids (Okubo 2005), submacular surgery (Matsuoka 2004) and transpupillary thermotherapy (TTT) (Vedantham 2005) have been published as single case reports indicating possible benefit for PCV. Other CNV therapies such as intravitreal steroids, radiotherapy, and translocation surgery have not been the focus of published reports in PCV patients.

1.3 RANIBIZUMAB AND PCV

There is well-established evidence suggesting that angiogenic factors, such as vascular endothelial growth factor (VEGF), play a major role in the pathogenesis of AMD-related CNV and in all forms of ocular neovascularization. Anti-VEGF therapy with aptamers (Gragoudas 2004) and with antibodies (Brown 2006, Rosenfeld 2006) has been demonstrated to be beneficial therapy for neovascular AMD. Surgically-excised PCV lesions demonstrate strong VEGF expression thus indicating a likely role for VEGF in PCV proliferation and exudation (Matsuoka 2004, Terasaki 2002). In addition, a significant increase of aqueous humor VEGF was found in eyes with exudative PCV (Tong 2006). This rationale has led to investigation of intravitreal anti-VEGF therapy for exudative PCV.

Gomi and coworkers (Gomi 2008) assessed the short-term efficacy of intravitreal bevacizumab (Avastin, Genentech Inc., San Francisco, CA) for 11 Asian eyes with PCV. One or two bevacizumab injections resulted in decreased OCT thickness at 1 month. This anatomical effect was lost at 3 months. Lesion size improved in one eye but residual or enlarged lesions were observed in the other 10 eyes. There were no

significant short-term effects on visual acuity. The authors proposed that a single bevacizumab injection is insufficient and that repeated bevacizumab injections or alternative anti-VEGF agents with greater retinal penetration or VEGF affinity may be required (Gomi 2008). Song and coworkers (Song 2009) similarly evaluated a single intravitreal bevacizumab injection in 19 Asian eyes and observed improvement at 3 months in both OCT retinal thickness and visual acuity. Fluorescein angiographic leakage was reduced at 3 months and partial polyp regression occurred in more than 50% of eyes. ICG angiography demonstrated no changes in the choroidal branching vessels suggesting that bevacizumab may not penetrate deeply enough to effect the more mature choroidal vascular abnormalities (Song 2009). Lai and coworkers (Lai 2008) treated 15 Asian PCV eyes with three monthly bevacizumab injections with or without PDT. At 3 months, visual acuity and OCT thickness improved. Persistent polyps were present in all eyes but subsequent PDT did lead to lesion regression in some eyes. The authors concluded that bevacizumab monotherapy has limited effect on lesion regression and proposed that combination bevacizumab with PDT may be optimal (Lai 2008). Lee and coworkers (Lee 2008) treated 8 Asian PCV eyes with bevacizumab alone and 4 Asian PCV eyes with combination bevacizumab and PDT. With mean followup of 17 weeks visual acuity, OCT thickness, and angiographic leakage improved. Partial or complete lesion regression occurred in most eyes. The authors proposed that bevacizumab monotherapy may be adequate therapy for less advanced lesions (Lee 2008).

There are just two published reports evaluating ranibizumab (Lucentis, Genentech Inc., SanFrancisco, CA) for PCV. Reche-Frutos and coworkers (Reche-Frutos 2008) noted that 3 monthly ranibizumab injections improved visual acuity and OCT thickness at 3 months follow-up in a Hispanic population. Polyp regression was observed in 9 of 13 eyes. The authors proposed that in comparison to bevacizumab, ranibizumab's deeper penetration may be responsible for the favorable polyp regression rate (Reche-Frutos 2008). Kokame and coworkers (Kokame 2009) treated 12 Asian PCV eyes with continuous monthly ranibizumab. Six month results indicated improved subretinal fluid, macular edema, and hemorrhage in the majority of eyes. One third of

eyes demonstrated decrease lesion size but branching choroidal vessels were unchanged. A press release from QLT Inc. (QLT Inc. 2009) reported results from the EVEREST prospective, randomized study evaluating ranibizumab monotherapy versus PDT monotherapy versus ranibizumab/PDT combination therapy for 61 eyes with Asian PCV. At 6 months the ranibizumab monotherapy, PDT monotherapy, and ranibizumab/PDT combination groups gained 9.2, 7.5, and 10.9 letters, respectively. Complete polyp regression occurred in 29%, 71% and 78% of eyes in the ranibizumab monotherapy, PDT monotherapy, and ranibizumab/PDT combination groups, respectively (QLT Inc. 2009).

The above data evaluating anti-VEGF therapy for PCV is limited by a relatively small number of treated eyes, short follow-up and absence of comparison groups. However, given the encouraging results of the above limited data along with the known favorable results of anti-VEGF therapy for neovascular AMD, as well as the overlap between exudative AMD and PCV, further evaluation of anti-VEGF therapy for PCV is needed. In addition, evaluation of anti-VEGF therapy for PCV has primarily occurred in an Asian population and little or no data exist for African-American and Caucasian populations. In fact, African-Americans are hardly represented in neovascular AMD anti-VEGF trials. Ethnic differences in PCV may well affect treatment responses due to genetic makeup, variances in the natural history of disease, and living environments.

We previously enrolled 20 non-Asian PCV eyes and evaluated intravitreal ranibizumab (0.3mg and 0.5 mg) for exudative PCV. Subjects included 16 African-Americans (12 female, 4 male) and 3 male Caucasians. The mean age was 63.6 years and the mean follow-up for the present ongoing study is 18 months. Mean baseline BCVA was 20/127 (range, 20/16-20/500) and CPT was 298 μm. Mean BCVA increased from baseline by 1.2 and 1.5 ETDRS lines at 12 and 24 months, respectively. Four of 14 eyes and 3 of 12 eyes gained ≥3 lines BCVA at 12 and 24 months, respectively. Mean CPT decreased from baseline by 53 μm and 67 μm at 12 and 24 months, respectively. Eyes received a mean of 7.2 injections during a mean follow-up of 19 months. Visually

significant ocular adverse events included cataract progression (n=3), mild vitreous hemorrhage (n=2), and macular hole (n=1). No systemic drug-related adverse events wereobserved.

Intravitreal ranibizumab was well tolerated in non-Asian patients with PCV; the majority of eyes experienced improvements in BCVA and CPT following ranibizumab treatment.

Clinical data of intravitreal anti-VEGF therapy indicate a need for multiple injections to maintain a beneficial effect for AMD, as well as for diabetic macular edema (DME). Similarly, for PCV, data outlined above indicates a need for multiple anti-VEGF injections and an absence of lesion regression with anti-VEGF monotherapy. Thus, dose-escalation of ranibizumab has been investigated using 1.0 and 2.0 mg doses for AMD and DME to assess if higher doses have greater efficacy and/or require less injections. Early studies for AMD and DME indicate higher doses are likely safe and may improve visual and anatomic outcomes. The HARBOR study (FVF4579g) is a phase III randomized trial (Genentech Inc., SanFrancisco, CA) comparing 2.0 mg to 0.5mg ranibizumab for neovascular AMD.

Evaluation of ranibizumab at higher doses is especially needed for PCV as limited data indicates lesions are recalcitrant to standard dose monotherapy. In addition, African Americans are underrepresented in AMD trials. We propose to evaluate high dose (2.0 mg) ranibizumab in previously treated and treatment naïve PCV eyes.

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 endophthalimits and retinal detatchment. Proper aseptic injection technique should always be used when administering ranibizumab. Increases in IOP have been noted within 60 minutes of intravitreal injection with ranibizumab. Therefore, IOP as well as perfusion of the optic nerve head should be monitored and

managed appropriately. Serious adverse events related to the injection procedure have occurred in <0.1% of intravitreal injections include endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract. Other serious ocular adverse events observed among ranibizumab-treated subjects and occurring in <2% of subjects included intraocular inflammation and increased IOP. The most common adverse reactions (reported ≥ 6% higher in ranibizumab-treated subjects than control subjects) were conjunctival hemorrhage, eye pain, vitreous floaters, increased IOP, and intraocular inflammation.,

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

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

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

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

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

The rates of key non-ocular SAEs and AEs, including Antiplatelet Trialists' Collaboration (APTC) ATEs, MI, and vascular death were similar for cohorts 1 and 2 and 0.3- and 0.5-mg dose groups. The incidence of MI and non-ocular hemorrhage was similar across Cohort 1 dose groups. APTC ATEs, including vascular and unknown deaths, nonfatal MI, and nonfatal cardiovascular accidents, were similar across dose groups. During the 12-month study period, 0.7% of subjects in the 0.3-mg

group and 1.2% of subjects in the 0.5-mg group suffered a stroke. The number of vascular deaths and deaths due to unknown cause did not differ across dose groups. Rates of key non-ocular SAEs in Cohort 2 were generally lower than those in Cohort 1.

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

2. OBJECTIVES

This Phase I study will investigate the safety and tolerability of intravitreally administered Ranibizumab in three initial monthly doses of 2.0 mg followed by a 9 month period of criteria-based, as-needed retreatment and 12 month off drug safety follow up in subjects with exudative polypoidal choroidal vasculopathy (PCV) for a total of 24 months.

2.1 Primary Objective

To investigate the safety and tolerability of 3 initial intravitreally administered injections of 2.0 mg Ranibizumab with a 9 month PRN treatement period and 12 month off drug safey follow up.

2.2 Secondary Objectives

1. *To investigate the changes from baseline in best corrected visual acuity (BCVA) at specified time points in subjects treated with 2.0mg intravitreal Ranibizumab.*
2. *To investigate the occurrence of ocular non-serious and serious adverse events through fluorescein and ICG angiography, fundus photography, spectral domain optical coherence tomography (OCT) at specified time points.*
3. *To investigate the occurrence of ocular non-serious and serious adverse events through direct and indirect ophthalmic examinations at specified time points.*

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Design-

Phase I Safety Study, Open-Label, Single-Center, Non-Randomized, Uncontrolled, Consecutive Case-Series.

Population and Sample-

Random sample of *20* consecutive adults, age >18 years, with polypoidal choroidal vasculopathy. Polypoidal choroidal vasculopathy (PCV) will be defined as CNV with occult characteristics on fluorescein angiography with saccular dilations and polypoidal interconnecting vascular channels on indocyanine green angiography and/or fluorescein angiography. PCV may be defined as a distinct clinical syndrome if the aneurysmal dilatations are visible clinically as reddish-orange and/or there are multiple hemorrhagic PED's. There may be some overlap with AMD in elderly patients. Elderly PCV patients may demonstrate drusen: however PCV may be defined in elderly patients when CNV is observed in peripapillary region, when drusen are not prominent, and when the patient is non-white, especially in African Americans (the likely major racial predilection for PCV in our patient population).

2.0 mg Ranibizumab cohort

Twenty eyes will be treated; PCV eyes may be treatment naïve or received previous PCV therapy greater than 30 days prior to enrollment. A maximum of *10* eyes that completed 24 month enrollment in our study evaluating 0.3 mg or 0.5mg Ranibizumab may be included. *Eyes will be treated with 3 monthly doses of 2.0 mg ranibizumab followed by 2.0mg ranibizumab on a PRN dosing regimen for 9 months.*

In the year 2 off drug treatment period subjects will be contacted via telephone interview for review of adverse events at month 18 and month 24.

Trial Schema-

Consented, enrolled patients will receive 3 consecutive monthly intravitreal 2.0 mg/0.5 ml Ranibizumab injections *with the first injection occurring at Day 0 and*

second and third injection occurring at month 1 and 2 respectively. The first injection will be followed by a 1wk post treatment safety assessment.

During the 3rd through 12th month, evaluations for retreatment will occur monthly (every 28-30 days). Retreatment with intravitreal 2.0 mg Ranibizumab or other therapies will be at the investigators discretion but guidelines for recommended retreatment are as follows:.

Retreatment with 2.0 mg Ranibizumab is recommended if any of the following criteria are met:

1. There is a ≥ 5 letter visual acuity loss from the previous visit if associated with disease activity on OCT (intraretinal edema, subretinal fluid, pigment epithelial detachment with fluid etc).

2. There is a ≥50 um increase in OCT CSF thickness from the previous visit.

3. There is persistent disease acitivity on OCT (intraretinal edema, subretinal fluid, pigment epithelial detachment with fluid etc).

From Month 3-12:

Consideration of alternative therapies, such as PDT, laser, or steroids will be at the investigators discretion but guidelines for alternative therapies are as follows:

Photodynamic therapy with visudyne or laser photocoagulation or intravitreal steroids may be considered as monotherapy or in combination with ranibizumab 2.0mg if the following criteria are met**:**

1.There is a ≥10 letter visual acuity loss from baseline or from a previous visit and 2 consecutive ranibizumab injections have been performed 1 and 2 months prior to the current visit and there is persistent acitivity on OCT *(intraretinal edema, subretinal fluid, pigment epithelial detachment with fluid etc).*

And for PDT or Laser (not applicable to steroids)

2. There is well defined hyperfluorescence on fluorescein angiography or ICG angiography that the investigator feels would be amenable to PDT or laser therapy.

Timing of Intervention and Assessments

Baseline/Day 0 (same day or different days):

Informed Consent, Medical and Ophthalmic History, Blood Pressure, Manifest Refraction, ETDRS Best Corrected Visual Acuity , IOP, dilated slit lamp examination with biomicroscopy and direct ophthalmologic exam, Routine Physical Exam, Fluorescein/ICG Angiography, OCT, and Fundus Photography, urine pregancancy test (women of childbearing potential only) Administration of 2.0mg Intravitreal Ranibizumab #1

1wk post treatment safety visit following intravitreal injection of Ranibizumab injection:

Snellen visual acuity with spectacles or pinhole, intraocular pressure, dilated slit lamp examination with biomicroscopy and indirect ophthalmoscopy, and blood pressure.

Month 1 & 2:

Blood Pressure, Manifest Refraction, ETDRS Best Corrected Visual Acuity , IOP, dilated slit lamp examination with biomicroscopy and direct ophthalmologic exam, Fluorescein/ICG Angiography, OCT, and Fundus Photography.

Intravitreal 2.0 mg Ranibizumab #2 and #3 respectively.

Month(s) 3 -12*:*

Blood Pressure, Manifest Refraction, ETDRS Best Corrected Visual Acuity, IOP, dilated slit lamp examination with biomicroscopy and direct ophthalmologic exam, Fluorescein/ICG Angiography (mandatory at months 3,6,9,12; optional at other visits), OCT, and Fundus Photography (mandatory at months 3,6,9,12; optional at other visits). Urine pregnancy test at month 12 for females of childbearing potential only.

From months 3 onward, at the discretion of the Investigator, Intravitreal 2.0 mg Ranibizumab, observation or non-study therapy (i.e. laser, intravitreal steroids, PDT etc.) may be administered. Other anti-VEGF agents including bevacizumab and standard dose (0.5mg) ranibizumab are excluded as optional therapies.

Month(s) 18 & 24

Telephone Interview to assess for adverse events. Subjects will not be eligible to receive 2.0mg Ranbizumab. Alternate treatments are at the investigators discretion during the off drug observational period.

Patient Accrual-

Subject Accrual per Month:1

Date of First Subject Enrolled: November 1, 2010

Date of Last Subject Enrolled: July 1, 2012

Date of Last Subject Completing Study: July 1, 2013

3.2 RATIONALE FOR STUDY DESIGN

The route (intravitreal injections) and 2.0 mg dose employed is currently evaluated in the HARBOR clinical trial evaluating 2.0 mg Ranibizumab in neovascular AMD. The three consecutive monthly injections will be followed by observation or therapy at the discretion of the investigator. Given the variable course of PCV and unknown response to 2.0 mg Ranibizumab, this regimen will allow the opportunity to evaluate Ranibizumab's safety and potential therapeutic efficacy, as well as to give the patient the opportunity to continue Ranibizumab or switch to an alternative non-anti-VEGF therapy. The *1* year duration of the study is of sufficient duration to determine significant safety issues as well as determine potential efficacy. The possible inclusion of patients completing month 24 follow up after receiving 0.3mg or 0.5 mg doses in our previous study, will determine significant safety issues as well as determine potential efficacy of the 2.0mg dose for this population, as well.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measure

The primary outcome measure for safety and tolerability is the following:

Incidence and severity of ocular and systemic adverse events. Examples include 30 letter loss, major subretinal hemorrhage,involving 75% or more of clinical macula (arcade to arcade), disease-related vitreous hemorrhage, injection-related endophthalmitis, retinal detachment, vitreous hemorrhage*, study drug/procedure* -

related uveitis, incidence and severity of other adverse events, as identified by physical examination, subject reporting, and changes in vital signs.

Secondary Outcome Measures

- Month 3, 6, 9, 12 best corrected visual acuity at 4 meters – rates for gain of 5,*10 and 15 or more letters*
- Month 3, 6, 9, 12 best corrected visual acuity at 4 meters- rates for loss of *15 or more letters*
- Median and Average best corrected visual acuity at 4 meters- gain/loss (letters) at 3,6,9,12 months.
- Mean change from baseline in central foveal thickness over time up to 12 months as assessed on OCT
- Mean change from baseline in macular volume overtime up to 12 months.
- Proportion of patients with no evidence of fluid from CNV as assessed by OCT at 12 months.
- Mean change from baseline in the total area of CNV fluorescein angiographic leakage overtime up to 12 months.
- Mean change from baseline in total area of ICG CNV lesion size (including polyps and deep choroidal vessels) overtime up to 12 months.
- Fluorescein and ICG angiograms and fundus photographs will also be graded at each time point compared to baseline as unchanged, resolved, improved, worsened, or cannot determine. For the FA and ICG evaluations, “resolved” will be defined as no leakage and no evidence of polyps or PCV choroidal lesion; “improved” will be defined as decreased leakage and/or decreased size, number, or hyperfluorescence of polyps and/or PCV choroidal lesion; and “worsened” will be defined as increased leakage and/or increased size, number or hyperfluorescence of polyps and/or PCV choroidal lesion. For fundus photography evaluations, “resolved” will be defined as no evidence of PED, subretinal fluid, hemorrhage, or hard exudate; improved will be defined as a decrease in PED,

subretinal fluid, hemorrhage, or hard exudate; and “worsened” will be defined increase in PED, subretinal fluid, hemorrhage, fibrosis, or hard exudates.

3.4 SAFETY PLAN

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

Serious adverse events of intravitreal injection such as endophthalmitis, retinal detachment and significant vitreous hemorrhage will be reported and monitored. Potential serious adverse events related to study drug such as significant uveitis, hypertension, thromboembolic event, or poor wound healing will be reported and monitored. Serious ocular adverse events such as major subretinal hemorrhage, vitreous hemorrhage and 6-line loss rate will be reported and monitored. Serious adverse events such as hospitalizations, surgeries, emergency room admissions and death will be reported and monitored.

Given the small population studied in this Phase I trial, it will be difficult to estimate the adverse event occurrences. Unmasking procedures or treatment recommendations related to drug or the study in particular are not necessary. Any death in the study population will lead to review and assessment while withholding drug injections for enrolled patients until fully reviewed. If two or more patients suffer thromboembolic events, drug injections will also be withheld for all enrolled patients until review and assessment occur.

3.5 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

4. MATERIALS AND METHODS

4.1 SUBJECTS

4.1.1 Subject Selection

Twenty subjects from one site in the United States will be enrolled. Subjects with active, exudative-PCV who have provided informed consent will be eligible. Subjects who completed the 24 month follow up in the original FVF3671s 0.3 mg or 0.5mg PCV protocol may enter the extension study with 2.0 mg without necessarily demonstrating active exudative PCV at enrollment. (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. *Any deviation/waivers granted regarding inclusion/exclusion criteria will be reviewed by the principal investigator and fully documented.*

- Males and Females >18 years of age. *Females of child bearing potential will undergo urine pregnancy testing* and be required to use appropriate methods of birth control.
- ICG and fluorescein angiographic characteristics consistent with active, leaking PCV with subfoveal lesions &/or subfoveal hemorrhage, lipid exudates, PED or fluid diagnosed within the past 6 months or diagnosed as newly active within the past 6 months. Subjects who completed the 24 month follow up in the original FVF3671s protocol may enter the extension study with 2.0 mg without necessarily demonstrating active exudative PCV at enrollment.
- Best-Corrected ETDRS Visual Acuity at 4 meters between 20/20 – 20/800
- Lesion size- no limitations
- Lesion Characteristics- leaking lesions consistent with PCV. No limitations on hemorrhage, fibrosis or atrophy.
- No therapy (includes non foveal laser, PDT, intravitreal steroids, TTT, radiotherapy, or anti-VEGF therapy) or intraocular surgery within the past 30 days for any condition.

- Clear ocular media to allow for photography/angiography.
- Ability to provide written informed consent and comply with study assessments for the full duration of the study

4.1.3 Exclusion Criteria

- Patients with features of age-related macular degeneration such as abundant drusen and demographic features consistent with this diagnosis.
- Allergy to Fluorescein, ICG, Iodine, Shellfish.
- Pregnancy (positive pregnancy test)
- 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
- Exclude other anti-VEGF agents as therapy options.
- History of previous subfoveal laser.
- Advanced glaucoma (IOP>25 or cup/disc ratio >0.8)
- Any condition in the opinion of the investigator that would interfere with disease status/progression or jeopardize patients' participation in the study.

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a non-randomized, open-label study of 2.0 mg Ranibizumab. Treatment assignment will be determined by baseline status of treatment naive vs. previously treated PCV eyes.

4.3 STUDY TREATMENT

4.3.1 Formulation

Ranibizumab 2.0mg is formulated as a sterile solution aseptically filled in a sterile 3-mL stoppered glass vial. Each vial contains 0.5 mL of 40 mg/mL (2.0mg dose level) ranibizumab aqueous solution (pH 5.5) with 10 mM histidine HCl, 10% trehalose

dihydrate, and 0.01% polysorbate 20, pH 5.5. The vial contains no preservative and is suitable for single use only. Vials should be protected from direct light.

For further details and molecule characterization, see the Investigator Brochure.

4.3.2 Dosage, Administration, and Storage

1. **Dosage-** 2.0 mg/0.05 ml Ranibizumab will be given monthly *from Day 0 through Month 2*, and then at the discretion of investigator no more frequent than monthly for months 3-12.
2. **Administration-** Intravitreal Injection *will only be given* at the Southeast Retina Center *location*.
   *See Appendix B for detailed pre-injection procedures.
3. **Storage-** Upon receipt, study drug kits will be refrigerated at 2°C - 8°C (36°F - 46°F). Vials will not be used beyond the expiration date. Ranibizumab vials will remain refrigerated and will not be frozen.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

Starting at month three (ranibizumab injection #1 at baseline, #2 at month 1, and #3 at month 2), treatment will occur at the discretion of the investigator. Observation is permitted as well as intravitreal 2.0 mg Ranizibumab as frequent as every month for months 3-12. Other anti-VEGF agents, such as Avastin or Macugen® or 0.5mg Ranibizumab, will not be permitted. At the discretion of the investigator, *starting* at month 3 thermal laser, photodynamic therapy with Visudyne®, intravitreal or periocular steroids are permitted, if necessary.

4.5 STUDY ASSESSMENTS

4.5.1 Assessments during the Treatment Period

See Section 3.1

4.5.2 Early Termination Assessments

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

4.6 SUBJECT DISCONTINUATION

Subjects have a right to withdraw from the study at any time. The subject may be withdrawn from the study for any reasons: if it is in the best interest of the subject, intercurrent illness, adverse events, or worsening condition. The Southeast Retina Center may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

All non serious and serious 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
- Macugen injection treatment in study eye
- SAE
- Any other safety concerns

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

4.7 STUDY DISCONTINUATION

This study may be terminated by Southeast Retina Center at any time. Reasons for terminating the study may include the following:

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

4.8 STATISTICAL METHODS

4.8.1 Analysis of the Conduct of the Study

There is no formal sample size calculation in this pilot study. As this is a phase I study, a sample size of 20 patients is chosen, making sure that it is feasible financially to conduct the study and logistically to complete the study within 2-3 years. If and when the study is planned for a phase II randomized control trial, appropriate statistical analysis will be determined.

4.8.2 Safety Analyses

All non serious and serious adverse events, angiographic assessments, physical examinations, vital signs, ocular examinations and visual acuity measurements from all 20 subjects will be utilized to summarize safety data for this pilot study.

4.8.3 Efficacy Analyses

1. **Primary Endpoint-** *See Section 3.3.1*
2. **Secondary Endpoints-** *See Section 3.3.2*

All subjects will be used in analysis of primary and secondary outcome parameters. Rates for the endpoints at the suggested time points will be presented as a % of the patients enrolled. Analysis of Variance will be used to assess for role of variables in for the endpoints. Variables will include # Ranibizumab injections, other therapies, baseline acuity, age, gender, etc.

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 extension study may be reviewed and summarized periodically while the study is ongoing to ensure the safety of subjects.

4.9 DATA QUALITY ASSURANCE

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

5. ASSESSMENT OF SAFETY

The safety of ranibizumab will be assessed through the collection and analysis of rates of primary safety outcomes.

5.1 ADVERSE EVENTS

All adverse events occurring from Day 0 through Month 12 or Early Withdrawal will be documented and assessed by the principal investigator. Subjects discontinuing early from the study should return for an early termination evaluation and will be contacted 7 days after their last injection or study visit to elicit for occurrence of adverse events (serious and nonserious).

For this protocol, an AE is any “on study” untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness) that occurs in a study subject, regardless of the suspected cause. “On study” refers to Day 0 through the last study visit.

Unchanged, chronic conditions are NOT AEs and will not be recorded. An exacerbation or worsening of a chronic condition should be recorded as an AE.

Both serious and nonserious AEs should be graded on a three-point scale (mild, moderate, severe) and reported in detail in the subjects clinic record.
The suggested definitions are as follows:

Mild: Discomfort noticed but no disruption of normal daily activity

Moderate: Discomfort sufficient to reduce or affect normal daily activity

Severe: Incapacitating with inability to work or perform normal daily activity

Using the following criteria, the investigator will also assess whether there is a reasonable possibility that study drug caused or contributed to the AE.

- Yes (possibly or probably)

  There is a clinically plausible time sequence between onset of the AE and study drug administration; and/or

  There is a biologically plausible mechanism for study drug causing or contributing to the AE; and

- No

  The AE may or may not be attributed to concurrent/underlying illness, other drugs, or procedures.

  A clinically plausible temporal sequence is inconsistent with the onset of the AE and study drug administration; and/or

  A causal relationship is considered biologically implausible.

5.2 BASELINE MEDICAL CONDITIONS

Chronic medical conditions present at enrollment that do not worsen in intensity or frequency during the trial shall not be considered as adverse events. These medical conditions will be adequately documented in the clinic record section medical history and/or physical examination. However, medical conditions present at enrollment that worsen in intensity or frequency during the treatment or post-treatment periods should be reported and recorded as AEs.

5.3 EVALUATIONS

Reviews of body systems will be performed.

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

5.4 VITAL SIGNS

Blood pressure will be measured at protocol-specified study visits (see Section 3.1).

5.5 PROCEDURES FOR RECORDING AND REPORTING ADVERSE EVENTS

5.5.1 Recording Adverse Events (see examples below)

To improve the quality and precision of acquired AE data, investigators should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording AEs. Do not use colloquialisms and/or abbreviations.
- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each events should be recorded as an individual AE).
- AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A “primary” AE, if clearly identifiable, generally represents the most accurate clinical term recorded. If a primary serious AE (SAE) is recorded, events occurring secondary to the primary event should be described as a narrative description of the case.

For example:

Orthostatic hypotension	→	Fainting and fall to floor	→	Head trauma	→	Neck pain

The primary AE is orthostatic hypotension.

5.5.2 Serious Adverse Events

An AE occurring **at any dose** (including overdose) should be classified as **SERIOUS** if:

- It resulted in death (i.e., the AE caused or led to death).
- It was life threatening (i.e., the AE placed the subject at immediate risk of death; it does not apply to an AE that hypothetically might have caused death if it were more severe).
- It required or prolonged inpatient hospitalization (i.e., the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion).
- It was disabling (i.e., the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions).
- It resulted in a congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or study drug prior to conception or during pregnancy).
- It does not meet any of the above serious criteria but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

SAE Reporting

For guidelines on reporting SAEs refer to section 5.5.5 Expedited IND Safety Reports.

- **5.5.3 Special Reporting Situations**

a. Death

Death is an outcome of an event. The **event** that resulted in the death should be recorded and reported in the clinic record and MedWatch and IND Forms.

b. Hospitalizations for Surgical or Diagnostic Procedures

The **illness** leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.

c. Pregnancy

d. **Thromboembolic events occurring in 2 or more of enrolled patients.**

5.5.4 Type And Duration Of Follow-Up After Adverse Events

All reported AEs should be followed until resolution or until the subject's participation in the study ends. Subjects who have an ongoing study drug–related SAE at study completion or at discontinuation from the study will be followed by the investigator or his or her designee until the event is resolved or determined to be irreversible, chronic, or stable by the investigator.

5.5.5 Regulatory Reporting Requirements for Principal Investigators Holding Their Own INDs

Investigators conducting studies under their own INDs are responsible for expedited Safety Reports and IND Annual Reports to the FDA.

Expedited IND Safety Reports:

For this **Investigator Sponsored IND Study**, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 312.32.

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

Fatal or Life-Threatening, Unexpected, Drug-related SAEs

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 **related** to the use of ranibizumab. Reports are to be telephoned or faxed to the FDA **within 7 calendar days** of the Investigator's knowledge of the event. Additionally, notify Genentech Medical Science Liaison by telephone **within 7** calendar days.

An **unexpected** adverse event is one that is not already described in the ranibizumab Investigator's Brochure (IB) This includes adverse events that have not been identified as life-threatening or causing a death as described in the IB, for example, elevated hepatic enzymes or hepatitis versus liver failure. This also includes unusual AEs not specifically described in the IB, for example, hemorrhage versus intraocular bleeding.

The 7-day telephone or fax report must be followed within 8 additional calendar days by a written IND safety report (MedWatch 3500A Form). Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. (See Appendix D for Analysis of Similar Events template). All safety reports previously filed to the IND concerning similar events should be analyzed. The significance of the new report in light of the previous, similar reports should be commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, the IRB, and all participating investigators within 15 calendar days of

the Investigator's knowledge of the event. The FDA prefers these reports on a MedWatch 3500A Form but alternative formats are acceptable (e.g. summary letter).

FDA Fax Number for IND Safety Reports:

1 (800) 332-0178

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

Genentech Medical Science Liaison:
Name: Lester Hosten
Tel: *2404010969*

AND:
Genentech Drug Safety at:
(650) 225-4682 or (650) 225-5288

AND:
IRB Contact information

RCRC IRB
706B Ben White Blvd., West
Austin, TX 78704
phone: +800 688 2132
fax: +512 685 6012

For questions related to Safety reporting, contact your Genentech Medical Science Liaison.

Serious, Unexpected, and Drug-related SAEs (not life-threatening or fatal)

A written IND Safety Report (described above) should also be produced for any unexpected SAE that is considered **related** to the use of ranibizumab but is **not life-threatening or fatal**. Investigators are required to notify the FDA, Genentech, the IRB, and all participating investigators by submitting the IND Safety Report within 15 days of the Investigator's knowledge of the event.

IND Annual Reports

All IND annual reports submitted to the FDA by the Investigator should be copied to Genentech. Copies of such reports should be mailed to:

Jim Nickas
Director of Drug Safety
Mailstop #84
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

5.5.5.1 MedWatch 3500A Reporting Guidelines: (See Appendix C for MedWatch form)

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:

- Identification of the primary event term
- 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

- If a death occurred, autopsy results if available

MedWatch forms can be obtained on-line at www.fda.gov/medwatch or by calling the FDA at 1-800-332-1088.

Follow-up information:

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

- Add to the original MedWatch 3500A report and submit it as follow-up
- Add documents and submit as follow-up with the original MedWatch 3500A form
- Summarize new information and fax it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted. (Patient identifiers are important so that new information is added to the correct initial report.)

Occasionally Genentech may contact the investigator for additional information, clarification, or current status of the subject for whom an adverse event was reported.

For questions regarding SAE reporting, you may contact the Genentech Medical Science Liaison.

6.0 INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

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

- FDA correspondence letter assigning an IND number or an IND waiver letter
- Original U.S. FDA Form 1572 (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

- 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
- Written documentation of IRB approval of protocol (identified by Southeast Retina Center (protocol number or title and date of approval) and informed consent document (identified by Southeast Retina Center protocol number or title and date of approval)
- A copy of the IRB-approved informed consent document
- Written documentation of IRB review and approval of any advertising materials to be used for study recruitment, if applicable
- Certified translations of IRB approval letters, pertinent correspondence, and approved informed consent document (when applicable)
- Current laboratory certification of the laboratory performing the analysis as well as current normal laboratory ranges for all laboratory tests.

6.2 STUDY COMPLETION

The following data and materials are required by Southeast Retina Center before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period (if applicable)
- 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 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 Southeast Retina Center and the drug manufacturer may inspect the records

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

6.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

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

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

Investigators are required to promptly notify their respective IRB/EC of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the investigator. Some IRBs or ECs may have other specific adverse event requirements that investigators are expected to adhere to. Investigators must immediately forward to their IRB/EC

any written safety report or update provided by Southeast Retina Center (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.

REFERENCES

Brown DM, Kaiser PK, Michels M, et al. for the ANCHOR study group. Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration. N. Engl. J. Med. 2006; 355:1432-1444

Chan et al. Photodynamic therapy with verteporfin for symptomatic polypoidal choroidal vasculopathy. Ophthalmol 2004;111:1576-1584.

Gragoudas ES, Adamis AP, Cunningham ET, Feinsod M, Guyer DR for the VEGF Inhibition Study In Ocular Neovascularization Clinical Trial Group. Pegaptanib in neovascular age-related macular degeneration. N Engl J Med 2004;351:2805-2816.

Gomi F, Sawa MD, Sakaguchi H, et al. The efficacy of intravitreal bevacizumab for polypoidal choroidal vasculopathy. Br. J. Ophthalmol. 2008;92:70-73.

Kokame GT, Yeung L, Lai JC. Continuous anti-VEGF treatment with ranibizumab for polypoidal choroidal vasculopathy: an interim 6-month report. Br. J. Ophthalmol. 2009. (epub)

Lai TY, Chan WM, Liu DT, Luk FO, Lam DS. Intravitreal bevacizumab (Avastin) with or without photodynamic therapy for the treatment of polypoidal choroidal vasculopathy. Br. J. Ophthalmol. 2008;92:661-666.

Lee SY, Kim JG, Joe SG, Chung H, Yoon YH. The therapeutic effects of bevacizumab in patients with polypoidal choroidal vasculopathy. Korean J. Ophthalmol. 2008;22:92-99.

Matsuoka M, Ogata N, Otsuji T, Nishimura T, Takahashi K, Matsumura M. Expresssion of pigment epithelium derived factor and vascular endothelial growth factor in choroidal neovascular membranes and polypoidal choroidal vasculopathy. Br J Ophthalmol 2004;88:809-815.

Nazimul H, Anjli H, Sundaram N. Role of photodynamic therapy in polypoidal choroidal vasculopathy. Indian J Ophthalmol 2005;53:101-104.

Nishijima et al. Laser photocoagulation of indocyanine green angiographically identified feeder vessels to idiopathic polypoidal choroidal vasculopathy. Am J Ophthalmol 2004;137:770-773.

Okubo et al. Visual improvement following trans-tenon's retrobulbar triamcinolone acetonide infusion for polypoidal choroidal vasculopathy. Graefes Arch Clin Exp Ophthalmol 2005;243:837-839.

QLT, Inc. 6-Month results from EVEREST study evaluating Visudyne therapy in patients with polypoidal choroidal vasculopathy. Press Release, December 9, 2009, Vancouver, Canada.

Reche-Frutos J, Calvo-Gonzalez C, Donate-Lopez J, et. al. Short-term anatomic effect of ranibizumab for polypoidal choroidal vasculopathy. Eur J Ophthalmol. 2008;18:645-648.

Rosenfeld PJ, Brown DM, Heier JS, et.al. for the MARINA Study Group. Ranibizumab for Neovascular Age-Related Macular Degeneration. NEJM 2006;355:1419-1431.

Silva et al. Polypoidal choroidal vasculopathy and photodynamic therapy with verteporfin. Graefe's Arch Clin Exp Ophthalmol 2005.

Spaide et al. Treatment of polypoidal choroidal vasculopathy with photodynamic therapy. Retina 2002;22:529-535.

Song JH, Byeon SH, Lee SC, Koh HJ, Kwon OW. Short-term safety and efficacy of a single intravitreal bevacizumab injection for the management of polypoidal choroidal vasculopathy. Ophthalmologica 2009;223:85-92.

Terasaki H, Miyake Y, Nakamura M, et al. Polypoidal choroidal

vasculopathy treated with macular translocation: clinical

pathological correlation. Br. J. Ophthalmol. 2002;86:321–327.

Tong JP, Chan WM, Liu TL et. al. Aqueous humor levels of vascular endothelial growth factor and pigment epithelium-derived factor in polypoidal choroidal vasculopathy and choroidal neovascularization. Am. J. Ophthalmol. 2006;141:456-462.

Uyama M, Matsubara T, Fukushima I, Matsunaga H, Iwashita K, Nagai Y, et al. Idiopathic polypoidal choroidal vasculopathy in Japanese patients. Arch Ophthalmol 1999;117:1035-1042.

Vedantham et al. Treatment of polypoidal choroidal vasculopathy with transpupillary thermotherapy: an interventional case report. Eye 2005;19:914-915.

Yannuzzi LA et al. Idiopathic polypoidal choroidal vasculopathy (IPCV). Retina 1990;10:1-8

Yannuzzi LA, Ciardella A, Spaide RF, Rabb M, Freund KB, Orlock DA. The expanding clinical spectrum of idiopathic polypoidal choroidal vasculopathy. Arch Ophthalmol 1997;115:478-485.

Yannuzzi LA, Wong DWK, Sforzolini BS, Goldbaum M, Tang KC, Spaide RF, et al. Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. Arch Ophthalmol 1999;117:1503-1510.

Yuzawa M, Mori R, Kawamura A. The origins of polypoidal choroidal vasculopathy. Brit J Ophthalmol 2005;89:602-607.

APPENDIX A
Study Flowchart

	Screen	Baseline (Day 0)	1 wk Safety Follow-up [c] after first dose only	Month 1	Month 2	Months 3 – 11	Month 12	Month 18 & 24
Informed consent	X							
Demographics	X							
Physical Examination and Medical History	X							
Vitals	X	X	X	X	X	X	X	
Urine Pregnancy Testing	X						X	
Ocular Exam [b]	X		X	X	X	X	X	
OCT SD	X	X		X	X	X	X	
FA/ICG	X	X		X	X	Xf	Xf	
Fundus photos	X	X		X	X	Xf	Xf	
Ranibizumab Injection		X		X	X	(X)[a]		
AE and ConMed Review		X	X	X	X	X	X	x
ETDRS Refraction & Visual Acuity (4 m)[e]	X	X	X	X	X	X	X	

Note:

[a] Ranibizumab injections for months 3-11, to be determined based on investigator's discretion.

[b] Ocular Exam includes IOP. Study eye only at safety assessments

[c] Safety Assessment post Injection to be performed 1 week after ranibizumab injection

[e] Refraction not required at 1 wk safety follow-up.

[f] F/A/ICG/photos performed at months 3,6,9 and 12 but may be performed monthly at investigator discretion

APPENDIX B
Pre-Injection Procedures for All Patients

The following procedures will be used to minimize the risk of potential adverse events associated with intravitreal injections (e.g., endophthalmitis). Aseptic technique will be observed by clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug (ranibizumab) preparation and administration. In addition to the procedures outlined below, any additional safety measures in adherence to specific institutional policies associated with intravitreal injections will be observed.

The following procedures (except where noted) will be conducted by the physician performing the intravitreal injection of study drug. Patients will self-administer antimicrobials (e.g., ofloxacin ophthalmic solution [Ocuflox®], gatifloxacin ophthalmic solution [Zymar®], moxifloxacin ophthalmic solution [Vigamox®], or trimethoprim-polymyxin B ophthalmic solution [Polytrim®]) four times daily for 3 days prior to treatment.

At the discretion of the investigator, the sites may use either ophthalmic drops or lidocaine injection for study eye anesthesia.

If using propacaine- or tetracaine-based ophthalmic drops for anesthesia, the injecting physician or technician (if applicable) assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4×4 sterile pads, a pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, 5% povidone iodine ophthalmic solution, ophthalmic antimicrobial solution (e.g., ofloxacin ophthalmic solution, trimethoprim-polymyxin B ophthalmic solution, moxifloxacin ophthalmic solution, or gatifloxacin ophthalmic solution single-use vial), and injection supplies. Note: The use of generic formulations or next-generation formulations of the antimicrobials listed above is permitted.

Procedure for Propacaine- or Tetracaine-Based Anesthesia:

- Instill two drops proparacaine or tetracaine-based ophthalmic drops into the study eye, followed by two drops of antimicrobial solution (e.g., ofloxacin ophthalmic solution, trimethoprim-polymyxin B ophthalmic solution, moxifloxacin ophthalmic solution, or gatifloxacin ophthalmic solution single-use vial).

- Wait 90 seconds.
- Instill two more drops of proparacaine- or tetracaine-based ophthalmic drops into the study eye
- Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.
- The physician will glove, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.
- Saturate a sterile, cotton-tipped applicator with proparacaine- or tetracaine-based drops and hold the swab against the planned intravitreal injection site for 10 seconds
- Use a sterile 4×4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.
- Instruct patient to direct gaze away from syringe prior to ranibizumab injection.

Procedure for Lidocaine-Based Anesthesia

If using lidocaine injection for anesthesia, physician or technician (if applicable) assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4×4 sterile pads, a pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, 0.5% proparacaine hydrochloride, 5% povidone iodine ophthalmic solution, 1% lidocaine for injection, ophthalmic antimicrobial solution (e.g., ofloxacin ophthalmic solution, trimethoprim-polymyxin B ophthalmic solution, moxifloxacin ophthalmic solution, or gatifloxacin ophthalmic solution single-use vial), and injection supplies.

Note: The use of generic formulations or next-generation formulations of the antimicrobials listed above is permitted.

- Instill two drops of 0.5% proparacaine hydrochloride into the study eye, followed by two drops of antimicrobial solution (e.g., ofloxacin ophthalmic solution, trimethoprim-polymyxin B ophthalmic solution, moxifloxacin ophthalmic solution, or gatifloxacin ophthalmic solution single-use vial).

- Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.
- The physician will glove, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.
- Saturate a sterile, cotton-tipped applicator with 0.5% proparacaine hydrochloride drops and hold the swab against the planned intravitreal injection site for 10 seconds in preparation for the subconjunctival injection of 1% lidocaine hydrochloride ophthalmic solution for injection (without epinephrine).
- Inject 1% lidocaine (without epinephrine) subconjunctivally.
- Use a sterile 4×4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.
- Instruct patient to direct gaze away from syringe prior to ranibizumab injection.

APPENDIX C
Preparation and Administration of Ranibizumab Injection

The injecting physician will prepare the ranibizumab injection as outlined below.

Vials of ranibizumab in aqueous solution should remain refrigerated at 2°C–8°C (36°F–46°F) until just prior to use. DO NOT FREEZE vials. Protect from direct light. Do not use beyond the expiration date. Dose solutions should be prepared immediately before dosing. Dose solutions are for single use only.

After preparing the study eye as outlined in Appendix B, withdraw 0.2-mL ranibizumab dose solution through a 5-μm filter needle. Remove the filter needle, replace it with a 30-gauge, 1/2-inch Precision Glide® needle, and **expel excess** ranibizumab **so that the syringe contains 0.05 mL of solution**. Insert the syringe through an area 3.5 to 4.0 mm posterior to the limbus, avoiding the horizontal meridian, and aiming toward the center of the globe. **The injection volume should be delivered slowly.** The needle should then be removed slowly to ensure that all drug solution is in the eye. **The scleral site for subsequent intravitreal injections should be rotated.** Refer to Appendix D for detailed post-injection procedures.

All injection materials (i.e., syringes, needles) will be discarded in a sharps container immediately following each ranibizumab injection. The ranibizumab drug kit (including the used vial) will be sealed by the injecting physician or technician with the “Do Not Tamper” seal provided in the drug kit.

A patient’s study eye will be monitored with a finger count test within 15 minutes of the ranibizumab injection by the physician. A measurement of IOP in the study eye will be obtained 30 (±5) minutes post-injection. If the IOP is increased ≥10 mmHg compared with the pre-injection IOP, then measure the IOP again at 60 (±10) minutes. The following table provides specific instructions for the preparation and administration ranibizumab in aqueous solution.

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Mfr Report #

UF/Importer Report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at Time of Event: or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight — ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   - ☐ Death: _____ *(mo/day/yr)*
   - ☐ Life-threatening
   - ☐ Hospitalization - initial or prolonged
   - ☐ Disability
   - ☐ Congenital Anomaly
   - ☐ Required Intervention to Prevent Permanent Impairment/Damage
   - ☐ Other: _____

3. Date of Event *(mo/day/year)*

4. Date of This Report *(mo/day/year)*

5. Describe Event or Problem

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
   #1
   #2

2. Dose, Frequency & Route Used
   #1
   #2

3. Therapy Dates *(if unknown, give duration)* from/to *(or best estimate)*
   #1
   #2

4. Diagnosis for Use *(Indication)*
   #1
   #2

5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot # *(if known)*
   #1
   #2

7. Exp. Date *(if known)*
   #1
   #2

8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# *(For product problems only)*
   – –

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Type of Device

3. Manufacturer Name, City and State

4. Model # | Lot #
   Catalog # | Expiration Date *(mo/day/yr)*
   Serial # | Other #

5. Operator of Device
   - ☐ Health Professional
   - ☐ Lay User/Patient
   - ☐ Other: _____

6. If Implanted, Give Date *(mo/day/yr)*

7. If Explanted, Give Date *(mo/day/yr)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   ☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

10. Device Available for Evaluation? *(Do not send to FDA)*
    ☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mo/day/yr)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. INITIAL REPORTER

1. Name and Address

Phone #

2. Health Professional? ☐ Yes ☐ No

3. Occupation

4. Initial Reporter Also Sent Report to FDA ☐ Yes ☐ No ☐ Unk.

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

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Medication and Device Experience Report

(Continued)

Refer to guidelines for specific instructions.

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

FDA USE ONLY

Page ____ of ____

F. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. **Check One** ☐ User Facility ☐ Importer
2. **UF/Importer Report Number**
3. **User Facility or Importer Name/Address**
4. **Contact Person**
5. **Phone Number**
6. **Date User Facility or Importer Became Aware of Event** *(mo/day/yr)*
7. **Type of Report** ☐ Initial ☐ Follow-up # ____
8. **Date of This Report** *(mo/day/yr)*
9. **Approximate Age of Device**
10. **Event Problem Codes** *(Refer to coding manual)*
Patient Code ____ – ____ – ____
Device Code ____ – ____ – ____
11. **Report Sent to FDA?** ☐ Yes ____ *(mo/day/yr)* ☐ No
12. **Location Where Event Occurred** ☐ Hospital ☐ Home ☐ Nursing Home ☐ Outpatient Treatment Facility ☐ Outpatient Diagnostic Facility ☐ Ambulatory Surgical Facility ☐ Other: ____ *(Specify)*
13. **Report Sent to Manufacturer?** ☐ Yes ____ *(mo/day/yr)* ☐ No
14. **Manufacturer Name/Address**

G. ALL MANUFACTURERS

1. **Contact Office - Name/Address** ***(and Manufacturing Site for Devices)***
2. **Phone Number**
3. **Report Source** *(Check all that apply)* ☐ Foreign ☐ Study ☐ Literature ☐ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other: ____
4. **Date Received by Manufacturer** *(mo/day/yr)*
5. (A)NDA # ____ IND # ____ PLA # ____ Pre-1938 ☐ Yes OTC Product ☐ Yes
6. **If IND, Give Protocol #**
7. **Type of Report** *(Check all that apply)* ☐ 5-day ☐ 15-day ☐ 10-day ☐ Periodic ☐ Initial ☐ Follow-up # ____
8. **Adverse Event Term(s)**
9. **Manufacturer Report Number**

H. DEVICE MANUFACTURERS ONLY

1. **Type of Reportable Event** ☐ Death ☐ Serious Injury ☐ Malfunction ☐ Other: ____
2. **If Follow-up, What Type?** ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. **Device Evaluated by Manufacturer?** ☐ Not Returned to Manufacturer ☐ Yes ☐ Evaluation Summary Attached ☐ No *(Attach page to explain why not)* or provide code: ____
4. **Device Manufacture Date** *(mo/yr)*
5. **Labeled for Single Use?** ☐ Yes ☐ No
6. **Evaluation Codes** *(Refer to coding manual)*
Method ____ – ____ – ____ – ____
Results ____ – ____ – ____ – ____
Conclusions ____ – ____ – ____ – ____
7. **If Remedial Action Initiated, Check Type** ☐ Recall ☐ Repair ☐ Replace ☐ Relabeling ☐ Notification ☐ Inspection ☐ Patient Monitoring ☐ Modification/ Adjustment ☐ Other: ____
8. **Usage of Device** ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. **If action reported to FDA under 21 USC 360i(f), list correction/ removal reporting number:**
10. ☐ **Additional Manufacturer Narrative** and / or 11. ☐ **Corrected Data**

FORM FDA 3500A (9/03) (Back)

Please DO NOT RETURN this form to this address.

APPENDIX D

Analysis of Similar Events Template for IND Safety Reports

IND Safety Report

Case Summary

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

PREVIOUS REPORTS

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

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

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

MCN	Reported Event	Submission Date

Or

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

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

Assessment of Relationship

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

Based on review of available data, Southeast Retina Center believes there is a reasonable possibility of a cause-and-effect relationship between administration of Ranizibumab 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 Southeast Retina Center does not believe that there is a reasonable possibility of a cause-and-effect relationship between administration of Ranizibumab and the occurrence of _____(insert AE).

Explain if warranted. Do not speculate.

Or

Based on review of available data, the Southeast Retina Center cannot establish or exclude the possibility of a cause-and-effect relationship between administration of Ranizibumab 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 Southeast Retina Center does not believe that changes to the conduct of this clinical trial are warranted. *This statement can be modified if changes to the conduct of the clinical trial are made*.