PROTOCOL

STUDY TITLE:	Phase I/II Prospective, Randomized, Double-blinded Study of Intravitreal Anti-VEGF therapy combined with Proton Beam Radiation versus Sham Irradiation in Treating Exudative Age-related Macular Degeneration
STUDY DRUG	Recombinant humanized anti-VEGF monoclonal antibody fragment (rhuFab V2, [ranibizumab, Lucentis]) Recombinant humanized anti-VEGF monoclonal antibody (bevacizumab, Avastin) Proton beam radiation
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1. BACKGROUND

1.1 PATHOPHYSIOLOGY

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss and legal blindness in the elderly population and the incidence is expected to increase dramatically in the next few decades as the baby boomer generation ages.[1] Exudative age-related macular degeneration (eAMD), a more severe and aggressive form of the disease, accounts for 90% of the patients with severe vision loss from AMD.[2] Exudative AMD is characterized by uncontrolled proliferation of neovascular tissue originating from the choroidal circulation deep to the retina which appears to be mediated in part by VEGF secreted by the overlying unhealthy macula.[3] Vision loss associated with eAMD results from retinal bleeding and swelling from the choroidal neovascular tissue (CNVM) and can be minimized using anti-VEGF therapy, such as ranibizumab (Lucentis) and bevacizumab (Avastin).[4,5] Ranibizumab is an active fragment of antibody to VEGF which was FDA-approved for treatment of eAMD. Bevacizumab is a whole antibody to VEGF which was FDA-approved for treatment of metastatic cancer but commonly used in treating eAMD since it is inexpensive ($50 per dose) and appears comparable in efficacy to the more costly ranibizumab (>$2000 per dose). Both anti-VEGF agents have a transient treatment effect, and sustained treatment benefit requires repeated monthly intravitreal injection and/or close monitoring for recurrence if therapy is temporarily stopped.[6] Although these two drugs appear to be well-tolerated, the trauma of each intravitreal injection carries a small risk of injection, bleeding, cataract formation and retinal detachment, etc, which may result in further vision loss. In addition, monthly treatment and/or monitoring eye examination are very time-consuming and costly. Thus, a highly effective treatment that is safe and with a more sustained treatment effect is needed. Such a treatment will have a huge impact on the quality and cost of eye care for the elderly.

Various therapies for eAMD are being explored currently in order to achieve a more sustained treatment effect, including ranibizumab combined with photodynamic therapy and newer drugs to inhibit VEGF.[7] These therapies all target the vascular component of the neovascular tissue growth associated eAMD. Histologic analysis of CNVM in eyes with eAMD revealed that a bulk of the tissue is composed of avascular fibrous tissue which can continue to grow and affect vision.[3] In animal tumor models and clinical oncology studies, a marked synergism between anti-VEGF therapy and chemotherapy and/or radiation has been noted.[8-10] Anti-VEGF therapy alone resulted in only a transient control of tumor growth. For sustained control of tumor growth, radiation had to be administered within 2 to 6 weeks of initiation of anti-VEGF therapy (R. Jain, personal communication). Based on these observations, it would be

important to investigate whether anti-VEGF therapy combined with radiation may have a similarly synergistic in treating eyes with eAMD.

Radiation as a possible therapy for eAMD has been investigated as a therapy in over 15 clinical trials during the past decade before the advent of anti-VEGF therapy.[11-26] The rationale for using radiation is that it affects proliferating cells and can treat both the vascular and avascular component of the CNVM associated with eAMD. Furthermore, animal studies have shown that low dose radiation (10Gy) can cause normalization of neovascular tissue such that vascular permeability is decreased.[27] In most clinical trials thus far, radiation was used as sole therapy for eAMD. Over 1000 patients have been treated in total in these trials using various doses and fractionation schedule.[11-26] Although the therapy was well tolerated with minimal serious adverse effect, visual benefit was modest and only noted in some clinical trials.

Currently, a phase 3 multicenter randomized prospective clinical trial has been started investigating the effect of intravitreal ranibizumab combined with radiation administered during vitrectomy surgery as epiretinal brachytherapy (CABERNET).[7] This study is based on the results of a pilot study that showed encouraging findings when epiretinal delivery of strontium-90 radiation to the macula during vitrectomy surgery was combined with anti-VEGF therapy (i.e. bevacizumab).[28] A sustained treatment effect was noted in 75% of eyes at 1 year and 38% of eyes have > 3 lines of visual improvement at 12 months follow-up. The visual benefit was comparable to patients who were treated with monthly ranibizumab therapy The limitation of this combination therapy is that vitrectomy surgery has to be performed in order to administer the radiation, exposing the eye to various complications of vitrectomy surgery such as retinal detachment, cataract, bleeding and infection. In addition, the actual dose of radiation delivered may not be well-controlled since it is dependent on the distance of the probe to the retinal surface which may vary from case to case depending on the surgeon.

Among the various modalities that can be used to deliver radiation to the macula, the safest and most efficient way is proton beam.[24] This form of radiation is the treatment of choice for treating small intraocular tumors since there is minimal lateral spread of radiation, allowing the same dose of radiation to be delivered using much fewer fractions.[30,31] In two previous studies, 16 and 24 Gy of proton beam was delivered in two fractions in patients with eAMD and was found to have no adverse effects after two years although radiation retinopathy occurred in 15% of subjects.[15,26] A possible trend toward visual benefit was noted with proton beam radiation alone although the visual outcome was not significantly better than untreated eyes.

Currently, we are conducting a pilot safety and feasibility study combining Lucentis with proton beam irradiation (24 Gy in 2 fractions 24 hours apart) in treating eyes with exudative eye related macular degeneration (IND # 100,481). Among the five subjects enrolled in the study, no safety concerns have been found, i.e. no radiation retinopathy was noted during the follow-up period ranging from 14 to 24 months. Among three eyes with newly diagnosed exudative age at enrollment, a sustained treatment effect has been noted with only 1.1 mean additional ranizibuzumab injections being needed, all for minimal macular edema on optical coherence tomography, during the 23 to 24 months follow-up period. All three eyes had > 3 lines of improvement in ETDRS best corrected vision acuity (BCVA) with BCVA of 20/40 or better with this combination therapy at month 12. Visual gain was maintained during the second year of the study except for 1 eye that had slow loss of vision enlargement of geographic atrophy. Among two eyes that had previously been treated with ranibizumab for exudative AMD at enrollment, both eyes required repeated ranibizumab therapy every 1 to 2 months for recurrent or persistent macular edema as was required before enrolling in the study. One of the two eyes had improvement of BCVA from 20/40 to 20/20 during the first year of this study which was maintained during the second year. The second eye which had been previously treated with 23 doses of ranibizumab prior to enrollment for persistent subretinal fluid associated with fibrovascular pigment epithelial detachment, had slowly increasing subretinal fluid and decreasing vision during the 14 months of this study despite almost monthly ranibizumab therapy. Based on this encouraging pilot data, the Food and Drug Administration recommended this randomized prospective phase I/II clinical trial to further evaluate the safety and efficacy of this combination therapy.

TABLE 1: Summary of Clinical Trials Using Radiation as Therapy for Exudative AMD.

Study	Dose	# Treated	Results
Zambarakji et al	8 x 2 Gy	83	62% lost 3 or more lines after 2 yrs
2006	12 x 2 Gy	83	53% lost 3 or more lines after 2 yrs
(f/u 2 yrs)			15% Radiation retinopathy
Proton beam			No visually significant complications
			No difference between two doses
Barak et al.	10x2 Gy	22 Treated	No difference in vision or FANG
2005	12x2 Gy	10 Treated	among various doses of radiation

(f/u 1 yr)	14x2 Gy	11 Treated	No Control
Stereotactic EBT	16x2 Gy	11 Treated	No significant complications
	18x2 Gy	8 Treated	
	20x2 Gy	32 Treated	
Marcus et al.	5 x 4 Gy	41 Treated	Smaller lesion, less fibrosis with Rx
2004		(10 sites)	Modest visual benefit at 6 mos
(f/u 1yr)		Randomized	No Visual Benefit at 1 yr
EBT		(88 enrolled)	1 case of mild radiation retinopathy
Prettenhofer et al.	14.4Gy	40 Treated	No visual benefit or FANG benefit
2004	25.2Gy	40 Treated	but no control
(f/u 4 yrs)			
Churei et al.	10x2 Gy	21 Treated	Vision loss--40% vs 81% (p 0.03)
2004		Nonrandomized	Improved FANG (p 0.03)
(f/u 2 yrs)		Controlled	No radiation complication
EBT			
Cuilla et al.	2x 8 Gy	20 Treated	No significant benefit with Rx
2002		Randomized	Trend toward visual stabilization
(f/u 1 yr)		Controlled	
Proton Beam		(37 enrolled)	
Hart et all	6 x 2 Gy	100 Treated	71% vs 61% 3 line loss (p 0.08)
2002		Randomized	
(f/u 2 yrs)		Controlled	
EBT		(199 enrolled)	
Valmaggia et al.	1 x 1 Gy	161 Treated	3.23 mean lines lost
2002	4 x 2 Gy	Randomized	1.73 mean lines lost (p 0.01)
(f/u 1.5yr)	4 x 4 Gy		1.93 mean lines lost (p 0.08)
EBT			No control or complications

Marcus et al. 2001 (f/u 1 yr) EBT	7 x 2 Gy	41 Treated Randomized (83 enrolled)	No significant difference
Flexal et al. 2000 (f/u 22 mos) Proton Beam	1 x 8 Gy 1 x 14Gy	24 Treated 24 Treated	44% stabilized or improved at 1 yr 75% stabilized or improved at 1 yr No control 1 case of vision loss from radiation with 14 Gy
RADS 1999 (f/u 1 yr) EBT	8 x 2 Gy	101 Treated Randomized Controlled (205 enrolled)	No benefit at 1 yr No radiation complication
Char et al. 1999 (f/u mean 17 mos) EBT	1 x 7.5Gy	13 Treated Randomized Controlled (27 enrolled)	Slightly less visual loss ($p<0.05$) No FANG difference No Complications
Spaide et al. 1998 EBT	5 x 2 Gy	91 Treated Nonrandomized Controlled 120 enrolled	No benefit or complications
Begink et al. 1998 (f/u 1 yr) EBT	4 x 6Gy	37 Treated Randomized Controlled (72 enrolled)	Less severe vision loss-52% vs 32% No complications
Yonemoto et al. 2000 (f/u mean 16 mos) Proton Beam	8 Gy 14Gy	21 Treated 27 Treated	36% Lesion control at 21 mos 89% Lesion control at 21 mos No complications; VA stable No control

Total # Subjects Treated 1062

1.2 TREATMENT OF EXUDATIVE AGE-RELATED MACULAR DEGENERATION

The current treatment options for treatment of exudative age-related macular degeneration include thermal laser photocoagulation, photodynamic therapy alone or in combination with intravitreal Kenalog, intravitreal Macugen, intravitreal Lucentis (ranibizumab) and intravitreal Avastin (bevacizumab).

1.3 RANIBIZUMAB AND BEVACIZUMAB FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION

Among the various treatments, the treatment of choice for patients with exudative age-related macular degeneration involving the fovea, the central macula, is anti-VEGF therapy, either ranibizumab (Lucentis) or bevacizumab (Avastin). The visual outcome of intravitreal anti-VEGF therapy is much better than that observed with other therapies.[4,5] Both drugs are used in equal frequency by clinicians to treat exudative AMD (PAT Survey by American Society of Retinal Specialists 2009). Although the relative efficacy of ranibizuamab and bevacizumab in treating exudative AMD is being investigated in several large multi-center prospective studies, most studies have shown that both drugs are effective and safe in treating eyes with exudative AMD.[4,5,44]

1.4 NONCLINICAL EXPERIENCE WITH RANIBIZUMAB AND BEVACIZUMAB

1.4.1 Nonclinical Pharmacokinetics

The pharmacokinetics of ranibizumab has been investigated in rabbits and cynomolgus monkeys following intravitreal and intravenous administration. In both species, following intravitreal administration, ranibizumab was cleared from the vitreous humor with a half-life of 2–3 days. Following single intravitreal administration to cynomolgus monkeys, retinal concentrations of ranibizumab were approximately one-third of vitreous concentrations and declined in parallel with vitreous concentrations. In humans, the intravitreal half-life of ranibizumab is estimated to be 7-8 days. Repeated intravitreal injections of ranibizumab can lead to detectable antibodies in serum in rabbits and cynomolgus monkeys.

The intravitreal dose of Bevacizumab (Avastin) most commonly used clinically is 1.25mg in 0.05ml. This dose was derived from consideration of the molecular weight and binding affinity differences between ranibizumab and bevacizumab. Bevacizumab 1.25mg is estimated to be roughly equivalent to ranibizumab 0.3 to 0.5mg in terms of number and affinity of the binding sites that are delivered to the eye.[32] The intravitreal half-life of bevacizumab is estimated to be twice that of ranibizumab due to the increased size of the moleculte (149kD versus 48kD) as well as the presence of the Fc portion. Pharmacokinetics of intravitreal bevacizumab have been studied in rabbits and cynomolgus macaques monkeys and found to be 4.3 days.[33-34] In both species, the drug was found to penetrate the full thickness of the retina into the choroidal layer.[35-37]

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).

Electrophysiologic studies in rabbits done at 3 hours to 4 weeks following intravitreal injection of 2.5mg of bevacizumab showed no evidence of retinal toxicity.[37]

1.4.3 Stability Studies

The stability of ranibizumab alone and in combination with verteporfin was assessed in vitro. The combination of ranibizumab and verteporfin in a 5% dextrose solution at concentrations of 500 μg/mL and 1.4 μg/mL, respectively, resulted in ranibizumab degradation and a decrease in ranibizumab capacity to bind VEGF. The ranibizumab degradation products have not been fully characterized. Although it is currently unknown if such degradation also occurs in vivo, sequential administration of verteporfin followed by ranibizumab with an intervening washout period will decrease the likelihood of loss of ranibizumab activity and degradation.

The stability of bevacizumab stored at 4 degrees C after aseptically aliquoting into multidose vials was studied. The drug was found to remain stable up to 6 months and remain stable if aseptic precautions are taken.[38]

1.5 CLINICAL EXPERIENCE WITH RANIBIZUMAB AND BEVACIZUMAB

Ranibizumab has been FDA-approved for treatment of exudative AMD as monotherapy. Please refer to the Ranibizumab Investigator Brochure or Lucentis™ Package Insert for additional details regarding clinical safety experience with ranibizumab. It is being clinically evaluated in several studies to study its effect in treating diabetic macular edema and retinal vein occlusion.

Bevacizumab was FDA-approved for systemic intravenous administration to treat patients with metastatic cancer (please refer to package insert for Avastin attached). Intravitreal bevacizumab has been used off-label successfully by clinicians since 2005 to treat eyes with exudative AMD and other causes of choroidal neovascularization.[39,40] It has been used successfully to treat macular edema and ocular neovascularization from retinal vein occlusion or diabetic retinopathy.[41-43] There are several large multi-center randomized clinical trials that are on-going to compare the efficacy of bevacizumab to ranibizumab in treating eyes with exudative AMD (e.g. CATT trial). The results are pending but retrospective non-randomized studies showed no difference in visual acuity in eyes with exudative AMD treated with ranibizumab versus bevacizumab.[44] No safety concerns have been noted in patients treated with intravitreous bevacizumab.[45] A recent survey of practicing retinal specialists showed that bevacizumab is used in equal frequency as ranibizumab in treating patients with exudative AMD (PAT survery, 2009).

2. OBJECTIVES

2.1 Primary Objective

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- To determine the safety and efficacy of proton beam radiation combined with ranibizumab (Lucentis) or bevacizumab (Avastin) in treating patients with exudative AMD

2.2 Secondary Objectives

- Evaluate best corrected visual acuity (BCVA) at months 0, 12 and 24 months.
- Evaluate the number of subjects with > 15 letters of visual improvement.
- Evaluate change in macular thickness as measured at baseline, 12 and 24 months by optical coherence tomography.
- Evaluate mean number of anti-VEGF injections needed at 12 and 24 months.

- Evaluate number of patients with loss of BCVA of ≥ 3 lines at 12 and 24 months.
- Evaluate the number of subjects with ≥3 lines of vision loss (among subjects with radiation retinopathy or papillopathy) at 12 and 24 months compared to baseline.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a prospective, randomized, double-blinded Phase I/II study of the safety and efficacy of intravitreally administered ranibizumab or bevacizumab in subjects with exudative age-related macular degeneration when combined with proton beam radiation.

Forty-five subjects will be consented and enrolled and randomized 1: 1: 1 to receive intravitreal anti-VEGF therapy (ranibizumab (0.5mg) or bevacizumab (1.25mg)) combined with sham, proton beam (16 Gy in 2 fractions) or proton beam radiation (24 Gy divided into 2 fractions). The accrual will occur over a 12 month period and subjects will be followed for 24 months. Thus, the study will be completed within 36 months of initiation of the study.

Each subject with newly diagnosed exudative AMD who received ranibizumab (0.5mg) or bevacizumab (1.25mg) intravitreally within 6 weeks as standard of care will be randomized 1: 1: 1 to sham irradiation, 16 Gy proton beam or 24 Gy proton beam in 2 fractions 24 hours apart. Randomization will be such that there is an equal number of subjects treated with ranibizumab versus bevacizumab for each radiation treatment group. The subjects will be following monthly by the treating retinal specialist and treated with a total of three monthly injections of ranibizumab (0.5mg) or bevacizumab (1.25 mg). Thereafter, each subject will be examined monthly with OCT as part of standard of care and repeat injection will be performed if there is any detectable recurrent or persistent macular edema or subretinal fluid noted on OCT, new retinal hemorrhage, or visual acuity is decreased by two lines or more. This criteria for retreatment is similar to the PRONTO and SAILOR studies and has become the standard of care (PAT Survey Result 2009).[6,44,46] Both the subject and treating ophthalmologist will be blinded to the treatment administered. Each subject will be treated with the same anti-VEGF drug for the duration of the study. Repeat fluorescein angiography will be performed annually and at the discretion of the treating retinal specialist.

Trial Schema is enclosed in Appendix A.

3.2 RATIONALE FOR STUDY DESIGN

Since synergism was noted between anti-VEGF therapy and radiation in animal and clinical oncology studies,[8-10] it is of interest to determine whether the effect of intravitreal ranibizumab or bevacizumab in treating exudative macular degeneration can be further enhanced by radiation. Based on our small pilot study and a pilot study combining bevacizumab with vitrectomy and epiretinal brachytherapy,[28] we need to determine whether the combination of anti-VEGF therapy and proton beam radiation is safe and effective among patients with this condition. The dose of radiation proposed for this study has been shown to be safe for treatment of exudative age-related macular degeneration when used alone.[26] Low dose of radiation has been shown to normalize neovascular tissue.[27] Proton beam is the safest way of administering radiation to the eye and can be administered in much fewer fractions than external beam radiation.[25] Since radiation retinopathy is seen about 1 to 2 yrs following radiation exposure, the patients will be followed for at least 2 year as part of this protocol. The enrolled subjects will be continued to be followed as part of usual care thereafter.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measures

The primary outcome measures for safety and efficacy are the following:

1. Incidence and severity of ocular adverse events, as identified by eye examination (including visual acuity testing).

2. Best corrected visual acuity (BCVA) at Months 0, 12 and 24.

3.3.2 Secondary Outcome Measures

- Number of subjects with $\geq$ 3 lines of BCVA improvement
- Change in macular thickness as measured at 12 and 24 months compared to baseline by optical coherence tomography.
- Number of intravitreal injections with anti-VEGF drugs needed at 12 and 24 months.

- Evaluate number of patients with loss of BCVA of $\geq$ 3 lines at 12 and 24 months.
- Evaluate the number of subjects with $\geq$ 3 lines of vision loss (among subjects with radiation retinopathy or papillopathy) at 12 and 24 months compared to baseline

3.4 SAFETY PLAN

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

- The potential side-effects of intravitreal anti-VEGF therapy for exudative age-related macular degeneration have been well characterized in previous clinical trials and studies.[4,5, 45] The only serious potential side-effect of intravitreal anti-VEGF injection is endopthalmitis which can occur in up to 1% of patients. This side-effect should not be increased by subjects treated concurrently with radiation. The potential side-effects of proton beam radiation include radiation retinopathy and papillopathy. The risk of serious vision loss from proton beam radiation using the dose and fractionation outlined in this protocol is negligible.[26] However, the combination therapy of intravitreal anti-VEGF and proton beam radiation has not been investigated previously except in our small on-going pilot study. Since some vascular endothelial growth factor is needed for normal vascular health, it is theoretically possible that inhibition of vascular endothelial growth factor may increase the risk of radiation retinopathy. However, it also is possible that anti-VEGF therapy may decrease the risk of visually significant radiation retinopathy since it has been used to treat radiation maculopathy. This safety and efficacy study will investigate whether any serious adverse side-effect is observed with this combination therapy and whether the treatment is effective. Enrolled subjects will be examined monthly for the 24 months duration of this study for any evidence of radiation retinopathy or papillopathy which may be visually significant. Any patient with retinal vascular disease or history of previous radiation exposure will be excluded from this study.
- One of the secondary endpoints of this study is the incidence of loss of BCVA of $\geq$ 3 lines at 12 and 24 months. This severe vision loss can occur as part of the natural progression of exudative macular degeneration. If this severe vision loss is due to radiation retinopathy, characteristic fundus and angiographic changes will be observed. Thus, it will be possible to determine

whether the vision loss is from that natural course of the condition or from adverse side-effect of the treatment.

- The incidence of endophthalmitis should be 1% or less based on previously published clinical data. The incidence of radiation retinopathy using the proton beam radiation dose outlined in this protocol is 15% based on a recent published report.[26] However, there should be no case of radiation retinopathy that is visually significant based on this previous report. A description of actions that will be taken if the adverse events occur.

    - Treatment recommendations: If visually significant radiation retinopathy with maculopathy is observed, subjects will be treated with laser therapy, intravitreal steroid therapy or anti-VEGF therapy as standard of care by the treating retinal specialist.

    - Supplemental clinical tests or procedures to complete diagnosis of the adverse even: Fluorescein angiography as needed.

    - Contingency review and assessment of the serious adverse events: If visually significant radiation retinopathy or papillopathy is observed, the Institutional Review Board and the Radiation Safety Committee at the University of California, Davis will be informed of the adverse event. Further enrollment in the study will be contingent on their recommendations.

- The number of subjects needed to observe specific effects or to show statistically significant results is usually much larger than the sample size for this study. Since this is a relatively small phase I/II study enrolling only 45 subjects with 30 eyes being treated with radiation combined with antiVEGF therapy, the study will be too small to detect adverse side-effects that may occur in less than 3% of subjects. In addition, it may be too small to determine whether this combination therapy is more effective than monotherapy with Lucentis unless the treatment effect of combination therapy is dramatically better than monotherapy. This small sample size was chosen based on the promising results of our pilot study and the reported results of other clinical trials using anti-VEGF therapy combined with low dose radiation. Thus, a

larger Phase III trial will be planned pending the results of this proposed study to obtain more safety and efficacy information of this combination therapy.

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

All subjects will be enrolled at the University of California, Davis, Eye Center, Department of Ophthalmology & Vision Science. The subjects will be recruited from the retina clinic at the University of California Davis Eye Center or the Veteran Administration Hospital Eye Clinic at Mather, CA, and followed monthly at these two study sites monthly as standard of care for the duration of the study.

Forty-five subjects from two sites in the United States will be enrolled. Eligible subjects who have provided informed consent. (See Appendix *A*, the study flow chart, for screening assessments.)

4.1.2 Inclusion Criteria

Subjects will be eligible if the following criteria are met:

- Ability to provide written informed consent and comply with study assessments for the full duration of the study
- Age $\geq$ 50 years
- Patient-related considerations
- Able to maintain follow-up for at least 24 months.
- Women must be postmenopausal without a period for at least one year.
- Diagnosed with Age-related Macular Degeneration (ARMD) with active subfoveal choroidal neovascular membrane (CNVM), newly diagnosed or treated with first dose of anti-VEGF therapy within 6 weeks of enrollment
- Visual acuity 20/40 to 20/400
- Lesion size < 12 Disc Area
- Submacular hemorrhage less than 75% of total lesion and not involving foveal center

- Submacular fibrosis less than 25% of total lesion
- Candidate for intravitreal anti-VEGF therapy

4.1.3 Exclusion Criteria

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

- Prior enrollment in the study
- Pregnancy (positive pregnancy test) or lactation
- 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
- Previous treatment with Photodynamic Therapy (PDT) or thermal laser in study eye
- Anti-VEGF therapy within 6 weeks
- Intravitreal or subtenon's Kenalog within 6 months
- Intraocular surgery within 3 months or expected in the next 6 months
- Current or planned participation in other experimental treatments for wet AMD
- Other concurrent retinopathy or optic neuropathy
- Other causes of CNVM, i.e. myopic degeneration or ocular histoplasmosis (POHS)
- Significant media opacity precluding adequate view of the fundus for exam, photography or OCT
- History of radiation therapy to the head or study eye
- Diabetes mellitus or hemoglobin A1c > 6
- Head tremor or h/o claustrophobia precluding positioning for proton irradiation
- Inability to maintain steady fixation with either eye
- History of Malignancy treated within 5 years
- Allergy to Fluorescein dye

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a prospective randomized double-blinded clinical trial. All enrolled subjects will be randomized 1: 1 : 1 to either sham irradiation, 16 Gy proton beam or 24 Gy proton beam, all administered in 2 fractions 24 hours apart. All eyes will receive intravitreal ranibizumab or bevacizumab as standard of care.

4.3 STUDY TREATMENT

4.3.1 Formulation

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile, 2-mL or 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%, α-trehalose dihydrate*,* and 0.01% polysorbate *20, pH 5.5.* Each vial contains no preservative and is suitable for single use only.

Bevacizumab, formulated as a sterile 25mg/ mL solution for intravenous administration, will be aseptically aliquoted in a sterile syringe by a compounding pharmacy or hospital in-patient pharmacy. Each syringe will be filled to deliver 0.05mL of 1.25mg of bevicizumab. The sterile solution of bevacizumab (25mg/mL) is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution. The 4mL intravenous solution is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP.

Further details and molecule characterization can also be found in the package inserts for the drugs.

4.3.2 Dosage, Administration, and Storage

a. Dosage

All subjects will be treated with intravitreal ranibizumab (0.5 mg) or bevacizumab monthly for 3 months. Thereafter, all subjects will be examined monthly and treated with the same intravitreal anti-VEGF drug (repeat injection) if there is any detectable recurrent or persistent macular edema or subretinal fluid noted on OCT, new retinal hemorrhage, or visual acuity is decreased by two lines or more attributed to progression of macular degeneration as standard of care. All subjects will also be treated with sham or proton beam radiation (16 or 24 Gy divided into two fractions at least 24 hrs apart) or sham radiation 2 to 6 weeks after the first anti-VEGF injection. Both the patient and treating ophthalmologist will be blinded.

b. Administration

Intravitreal administration of anti-VEGF therapy will be performed by treating retinal specialists using a technique and protocol which has become standard of care. Briefly, the eye will be anesthesized with topical lidocaine and prepped using topical 5% betadine solution. A sterile lid speculum will be used to open the eye. Anti-VEGF drug will be administered 4mm behind the limbus using a TB syringe attached to a 30 gauge needle. A volume of 0.05cc will be injected per eye per injection. Visual acuity of at least Counting finger after injection will be confirmed. If visual acuity is worse than counting finger, intraocular pressure

measurement and funduscopy will be promptly performed. Paracentesis will be performed at the discretion of the treating ophthalmologist.

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 and bevacizumab syringes or vials should remain refrigerated. Protect from direct sunlight. Ranibizumab will be stored in original carton until time of use.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

Subjects may be treated with topical antibiotics for 1 day before and up to 7 days after each intravitreal injection at the discretion of the treating ophthalmologist. Subjects may continue to receive all medications and standard treatments administered for their conditions at the discretion of their treating physician.

4.5 STUDY ASSESSMENTS

4.5.1 Assessments during the Treatment Period

All subjects will be instructed to contact the investigator or treating physician by telephone promptly for any worsening vision or eye pain to ensure that they are not experiencing any serious adverse side-effect from the injection. All subjects will be examined monthly by the treating retinal specialist to ensure no serious adverse side-effect has occurred and to determine whether repeat anti-VEGF injection will be needed after the first three months. As outlined in Appendix A, all subject will sign an informed consent and a medical release statement at enrollment such that copies of the eye examination, including visual acuity, OCT, fundus photography and fluorescein angiography at baseline and each monthly follow-up visit can be obtained from the treating retinal specialist by the study investigators.

4.5.2 Early Termination Assessments

Subjects who withdraw from the study prior to completion should return for an early termination evaluation 30 days (± 7days) following the last injection/study visit for monitoring of all adverse events (serious and nonserious) if possible. 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 Department of Ophthalmology & Vision Science at the University of California, Davis, Medical Center 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
- Intraocular surgery in the study eye
- Investigator determination that it is not in the best interest of the subject to continue participation
- Pregnancy
- Verteporfin PDT treatment in the study eye
- Pegaptanib sodium injection treatment in either 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. In addition, the subject will be treated for the SAE based on the standard of care for that condition. If a subject is discontinued from the study for reasons other than SAE directly related to the treatment proposed in this proposal, an additional subject will be enrolled.

4.7 STUDY DISCONTINUATION

This study may be terminated by The University of California, Davis, Medical 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 a phase I/II study. As this is a phase I/II study with three treatment groups, a sample size of forty-five patients is chosen, to make sure that it is feasible financially to conduct the study and logistically to complete the study within 3 years.

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

4.8.2 Safety Analyses

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

4.8.3 Efficacy Analyses

a. Primary Endpoint

All forty-five subjects enrolled in this study will be included to determine the safety and efficacy of proton beam radiation combined with intravitreal anti-VEGF therapy in treating patients with exudative AMD. The fifteen subjects treated with anti-VEGF therapy and sham irradiation will be compared to fifteen subjects treated with anti-VEGF therapy and 16 Gy of proton beam and fifteen subjects treated with anti-VEGF therapy and 24 Gy of proton beam. Best corrected visual acuity (BCVA) at Months 0, 12 and 24 will be used as a primary measure of efficacy.

Incidence and severity of ocular adverse events, as identified by eye examination (including visual acuity testing) will be evaluated. In addition, % of subjects with radiation retinopathy and papillopathy at 12 and 24 months will be determined.

b. Secondary Endpoints

- Number of subjects with $\geq$ 3 lines of visual improvement

- Change in macular thickness as measured at baseline and 12 and 24 months by optical coherence tomography.
- Number of anti-VEGF injections needed at 12 and 24 months.
- Evaluate number of patients with loss of BCVA of $\geq$ 3 lines at 12 and 24 months.
- Evaluate the number of subjects with $\geq$ 3 lines of vision loss (among subjects with radiation retinopathy or papillopathy) at 12 and 24 months compared to baseline

Subjects who prematurely withdraw from the study will be excluded from the data analysis unless the withdrawal was determined to be due to SAE directly related to the treatment proposed in this study. If severe vision loss (>15 letters of vision loss) occurred due to SAE related to the treatment proposed, this information will be included in the data analysis.

4.8.4 Missing Data

Analyses of efficacy and safety will be based on available cases, without imputation for missing values.

4.8.5 Interim Analyses

No formal schedule of interim analyses is planned. Reports of adverse events from this study may be reviewed and summarized periodically while the study is ongoing to ensure the safety of subjects.

4.9 DATA QUALITY ASSURANCE

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

5. ASSESSMENT OF SAFETY

The safety of ranibizumab or bevacizumab combined with proton beam radiation will be assessed through monthly examination of the subjects until month 24.

5.1 ADVERSE EVENTS

AEs that start on Day 0 through the last study visit will be recorded on the appropriate AE pages of the CRF. 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 should not be recorded on the AE pages of the CRF. 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 on the appropriate AE page of the CRF.

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, investigators also need to 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

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

- No

  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

It is not necessary to complete an AE CRF page for chronic medical conditions present at enrollment that do not worsen in intensity or frequency during the trial. These medical conditions should be adequately documented on the appropriate page of the CRF (medical history and/or physical examination). However, medical conditions present at enrollment that worsen in intensity or frequency during the treatment or posttreatment periods and ongoing AEs that started during the previous study 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 PROCEDURES FOR RECORDING AND REPORTING ADVERSE EVENTS

5.4.1 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

Investigators must report all SAEs to the FDA and local IRB within 48 hours of observing or learning of the event. For initial SAE reports, investigators should record all case details that can be gathered within 48 hours on the SAE page of the CRF.

5.4.3 Special Reporting Situations

a. Death

Death is an outcome of an event. The **event** that resulted in the death should be recorded and reported on the SAE pages of the CRF.

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

Animal reproduction studies have not been conducted with ranibizumab or bevacizumab. It is also not known whether ranibizumab can cause fetal harm when administered to pregnant women or can affect reproduction capacity. Any pregnancy occurring during study treatment should be reported and the subject removed from the study.

5.4.4 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.

5.4.5 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 anti-VEGF therapy or proton beam irradiaiton. Reports are to be telephoned or faxed to the FDA **within 7 calendar days** of the Investigator's knowledge of the event.

An **unexpected** adverse event is one that is not already described in the ranibizumab and bevacizumab package inserts. 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, preferably 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

AND submitted to:
University of California, Davis, Institutional Review Board

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 or bevacizumab or proton beam but is **not life-threatening or fatal**. Investigators are required to notify the FDA, the IRB, and all participating investigators by submitting the IND Safety Report within 15 days of the Investigator's knowledge of the event.

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.)

6.0 INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study, the following documents must be on file with The University of California, Davis, Medical 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 The University of California, Davis, Medical Center, protocol number or title and date of approval) and informed consent document (identified by University of California, Davis, Medical 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
- The informed consent document and any advertising materials must also be reviewed and approved by the University of California, Davis, Medical Center Legal Department.
- 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 The University of California, Davis, Medical Center before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period (if applicable)
- Case Report Forms properly completed by appropriate study personnel and signed and dated by the investigator (if applicable)
- Copies of protocol amendments and IRB approval/notification (if applicable)
- A summary of the study prepared by the Principal Investigator (will accept IRB summary close letter) (if applicable)
- All regulatory documents (e.g., curricula vitae for each Principal Investigator, U.S. FDA Form 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 [University of California Davis Medical 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 [University of California Davis Medical Center] (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.5 CASE REPORT FORMS

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

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

6.6 STUDY DRUG ACCOUNTABILITY

Not applicable since ranibizumab and bevacizumab will be administered as standard of care by treating ophthalmologist.

6.7 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, the drug manufacturer and the IRB/EC for each study site, if appropriate.

6.8 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

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APPENDIX A
Study Flowchart

	Base-line	1-6 wks	1 m	2 m	3 m	4 m	5 m	6 m	7 m	8 m	9 m	10 m	11 m	12 m	13 m	14 m	15 m	16 m	17 m	18 m	19 m	20 m	21 m	22 m	23 m	24 m
Informed Consent	X																									
Medical History	X																									
BCVA	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthal Exam	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus Photos	X													X												X
Fluores Angio	X													X												X
OCT	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Axial Length Ultra-sonography	X																									
Anti-VEGF Injection	X		X	X	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Mask Fitting*		X																								
Proton Beam or Sham* (2 Tx)		X																								

* 16 or 24 Gy of proton beam or sham will be administered in 2 fractions 24 hours apart.

Anti-VEGF therapy, either Ranibizumab (0.5 mg) or bevacizumab (1.25mg) repeat injection will be performed if there is any detectable recurrent or persistent macular edema or subretinal fluid noted on OCT, new retinal hemorrhage, or visual acuity is decreased by two lines or more.

Procedures highlighted in bold will be performed by the investigators at the University of California Davis. The remaining procedures will be done by the treating ophthalmologists as standard of care at the University of California Davis Eye Center or the Mather VA Hospital Eye Clinic.

Medic[illegible]
Experience Report
(Continued)

an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

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FDA USE ONLY

Refer to guidelines for specific instructions.

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 ☐ Outpatient Diagnostic Facility ☐ Home ☐ Ambulatory Surgical Facility ☐ Nursing Home ☐ Outpatient Treatment 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 ☐ Notification ☐ Repair ☐ Inspection ☐ Replace ☐ Patient Monitoring ☐ Relabeling ☐ 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

The public reporting burden for this collection of information has been estimated to average one hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
MedWatch; HFD-410
5600 Fishers Lane
Rockville, MD 20857

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

product caused or contributed to the event.

☐ Yes ☐ No

Report to FDA ☐ Yes ☐ No ☐ Unk.

FORM FDA 3500A (9/03)