PROTOCOL

STUDY TITLE:	*Evaluation of Inflammation and Pain Post Injection of Ranibizumab vs. Aflibercept in Patients with Diabetic Macular Edema* *Phase II*
STUDY DRUG	*Recombinant humanized anti-VEGF monoclonal antibody fragment (rhuFab V2 [ranibizumab])* *Recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 (aflibercept)*
SPONSOR	*Sierra Eye Associates* *950 Ryland Street, Reno, Nevada, 89511*
INVESTIGATOR	*Arshad Khanani M.D.*
SUB-INVESTIGATORS	*Gregory Cohen M.D.*
DATE FINAL:	*14-Dec-2014*
AMENDMENT :	

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1. BACKGROUND

1.1 PATHOPHYSIOLOGY

Diabetic Macular edema (DME) is caused by accumulation of fluid and exudates in the macula. It is mediated by the production of VEGF and other growth factors in response to ischemia. In patients with diabetes for over 10 years, the prevalence of DME is estimated at one in four in type 2 diabetics and one in five people with type 1 diabetics.

1.2 TREATMENT

There are several options available for the treatment of Diabetic Macular Edema including focal laser, grid laser and ozurdex injection. Lucentis 0.3mg and Eylea 2.0mg are also FDA approved for DME

1.3 RANIBIZUMAB AND AFLIBERCEPT

Ranibizumab 0.3mg is FDA approved treatment and is available to patients with Diabetic Macular Edema.

Ranibizumab is a recombinant humanized monocolonal antibody that binds to human vascular endothelial growth factor A (VEGF-A). The binding of Ranibizumab to VEGF-A inhibits the interaction of VEGF-A with its receptors on the surface of the endothelial cells, resulting in reduced vascular leakage and new blood vessel proliferation.

Aflibercept 2.0mg is FDA approved for DME . Aflibercept acts as a soluble decoy receptor that binds to human vascular endothelial growth factor A (VEGF-A) and placental growth factor (PIGF). VEGF-A and PIGF act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. Inhibiting these factors with Aflibercept results in decreased neovascularization as well as vascular permeability.

1.4 NONCLINICAL EXPERIENCE WITH RANIBIZUMAB

1.4.1 Nonclinical Pharmacokinetics

The pharmacokinetics of ranibizumab have been investigated in rabbits and cynomolgus monkeys following intravitreal and intravenous administration. In both species, following intravitreal administration, ranibizumab was cleared from the vitreous humor with a half-life of 2–3 days. Following single intravitreal administration to cynomolgus monkeys, retinal concentrations of ranibizumab were approximately one-third of vitreous concentrations and declined in parallel with vitreous concentrations. In humans, the intravitreal half-life of ranibizumab is estimated to be 9 days. Repeated intravitreal injections of ranibizumab can lead to detectable antibodies in serum in rabbits and cynomolgus monkeys.

1.4.2 Nonclinical Toxicology

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

1.4.3 Nonclinical Data Supporting the Anti-Edema Activity of Ranibizumab

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

1.5 CLINICAL EXPERIENCE WITH RANIBIZUMAB

The safety and efficacy of LUCENTIS were assessed in two randomized, double-masked, 3-year studies in patients with DME. The studies were sham-controlled through Month 24. Patient age ranged from 21 to 91 years, with a mean age of 62

years. A total of 759 patients (LUCENTIS 0.3 mg, 250 patients; LUCENTIS 0.5 mg, 252 patients; sham, 257 patients) were enrolled, with 582 (77%) completing through Month 36.

In Studies DME-1 and DME-2, patients received monthly LUCENTIS 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections during the 24-month controlled treatment period. From Months 25 through 36, patients who previously received sham were eligible to receive monthly LUCENTIS 0.5 mg and patients originally randomized to monthly LUCENTIS 0.3 mg or 0.5 mg continued to receive their assigned dose. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 24-month treatment period or panretinal photocoagulation (PRP) as needed. Through Month 24, macular focal/grid laser treatment was administered in 94 of 250 (38%) patients treated with LUCENTIS 0.3 mg and 185 of 257 (72%) patients treated with sham; PRP was administered in 2 of 250 (1%) patients treated with LUCENTIS 0.3 mg and 30 of 257 (12%) patients treated with sham.

In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

1.6 CLINICAL EXPERIENCE WITH AFLIBERCEPT FOR DME

Aflibercept 2.0mg injection has been FDA approved for DME after the completion of VIVID-DME and VISTA-DME clinical trials. The VIVID-DME and VISTA-DME trials were similarly designed, randomized, double-masked, active control trials to evaluate the safety and efficacy of EYLEA in patients with DME. Patients in both trials were randomized to receive either EYLEA 2 milligrams (mg) monthly, EYLEA 2 mg every two months (after 5 initial monthly injections), or the comparator treatment of laser

photocoagulation.

In the VIVID-DME trial, after one year patients receiving EYLEA 2 mg monthly had a mean change from baseline in BCVA of 10.5 letters ($p < 0.0001$ compared to laser) and patients receiving EYLEA 2 mg every other month (after 5 initial monthly injections) had a mean change from baseline in BCVA of 10.7 letters ($p < 0.0001$ compared to laser), compared to patients receiving laser photocoagulation who had a mean change from baseline in BCVA of 1.2 letters.

In the VISTA-DME trial, after one year patients receiving EYLEA 2 mg monthly had a mean change from baseline in best-corrected visual acuity (BCVA) of 12.5 letters ($p < 0.0001$ compared to laser) and patients receiving EYLEA 2 mg every other month (after 5 initial monthly injections) had a mean change from baseline in BCVA of 10.7 letters ($p < 0.0001$ compared to laser), compared to patients receiving laser photocoagulation who had a mean change from baseline in BCVA of 0.2 letters.

In these trials, EYLEA was generally well tolerated with a similar overall incidence of adverse events (AEs), ocular serious AEs, and non-ocular serious AEs across the treatment groups and the laser control group. Arterial thromboembolic events as defined by the Anti-Platelet Trialists' Collaboration (non-fatal stroke, non-fatal myocardial infarction, and vascular death) also occurred at similar rates across the treatment groups and the laser control group. AEs were typical of those seen in other studies in patients with diabetes receiving intravitreal anti-VEGF therapy. The most frequent ocular treatment emergent AEs (TEAEs) observed in the VIVID-DME and VISTA-DME trials included conjunctival hemorrhage, eye pain, and vitreous floaters. The most frequent non-ocular TEAEs included hypertension and nasopharyngitis, which occurred with similar frequency in the treatment groups and the laser control group.

2. OBJECTIVES

This study is designed to compare the post injection inflammation and pain seen after intravitreal injections of ranibizumab 0.3mg and aflibercept 2.0mg in patients with DME.

We will be evaluating patients (1-7 days) post injections for:

1. Intraocular inflammation (defined as anterior chamber and/or vitreous cells)
2. Pain (as measured on a standardized pain scale).

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open-label, Phase II study of post injection pain and inflammation after intravitreally administered ranibizumab and aflibercept in 100 subjects with Diabetic Macular Edema. Treatment naïve and experienced patients will be enrolled. Treatment experienced patients with history of anti-vegf injections will be eligible as long as they have not received any intravitreal injection in the 3 months prior to the study visit. Patients will be randomized to receive either Lucentis 0.3 mg or Eylea 2.0 mg, and followed for a week. A non-injecting masked physician who is blinded to the treatment drug will evaluate the patient at baseline before the injection and then within 1-2 days and 5-7 days after the injection for anterior chamber and vitreous cells. Pain will also be recorded at these visits using a standardized pain scale.

Consented, enrolled subjects will receive open-label intravitreal injection of either 0.3 mg ranibizumab or 2.0 mg aflibercept. A standard intravitreal injection protocol will be followed. Patients will be revaluated at baseline, 1-2 days and 5-7 days post injections. A non-injecting physician will evaluate the patients for anterior chamber and vitreous inflammation; this physician will be blinded about the specific treatment. Anterior chamber inflammation is described as any cell or flare in the anterior chamber. These will be evaluated using Standardization of Uveitis Nomenculature (SUN)[6] working group classifications (see Appendix D). Pain score will be evaluated using a

Numerical Rating Scale. (See Appendix E) Each patient will have a standard script verbally read to them at their visit, and asked to rate their pain based on this scale. Their answers will be captured in a CRF. Patients will also be contacted via telephone by the study coordinator between the first 2 visits to inquire about pain, and will go through this same pain scale over the phone, using the same script. If the patient complains of increased pain score since visit #1, another visit will be initiated prior to the scheduled visit #2

We plan to enroll 100 patients in the study. We plan to recruit 8 patients per month and finish the study in 13 months.

3.2 RATIONALE FOR STUDY DESIGN

Patients will be injected with ranibizumab 0.3mg and aflibercept 2.0mg. Almost all complaints after intravitreal injections occur during the first week post injection, especially within the first 48 hours. Therefore, we plan to evaluate patients 1-2 days post injection and 5-7 days post injection[1,2,3,4,5].

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measures

1. Evidence of anterior chamber and vitreous inflammation at visit #1 and #2 compared with baseline

3.3.2 Secondary Outcome Measures

1. Pain post injection as measured on a standardized pain scale at visit #1 and #2. compared with baseline

3.4 SAFETY PLAN

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

Patients are treated with the suggested study medications on a daily basis in our clinic, routine safety protocols will be used to notify patients about the adverse reactions to the suggested medications.

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

100 subjects with Diabetic Macular Edema from **1** site in the United States will be enrolled. Eligible subjects will be administered and provided with a copy of an informed consent form. (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 ≥ **21** years
- Exam and OCT confirming Diabetic Macular Edema
- Visual Acuity of 20/400 or better
- No history of post injection pain or inflammation in the past

4.1.3 Exclusion Criteria

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

- History of Endophthalmitis in either eye
- Current inflammation in either eye
- Uncontrolled or symptomatic Dry Eye Syndrome
- Intravitreal injection less than 3 months ago
- History of Anterior or Posterior Uveitis
- History of post injection pain with prior treatments
- Recent thromboembolic event (<3 months)
- Pregnancy (positive pregnancy test) or lactation

- Premenopausal women not using adequate contraception. The following are considered effective means of contraception: surgical sterilization or use of oral contraceptives, barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel, an IUD, or contraceptive hormone implant or patch.

4.2 METHOD OF TREATMENT ASSIGNMENT

Patients will be randomly assigned to either ranibizumab or aflibercept treatment group. The physician evaluating for anterior chamber and vitreous inflammation will be blinded about the treatment given to the patient. The investigator and the patients will be aware of the treatment given. Patients will be randomized by drawing the medicine name from an envelope.

4.3 STUDY TREATMENT

4.3.1 Formulation

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile,3-mL stoppered glass vial. Each vial is designed to give 0.05 ml with resulting 0.3mg dose. Each vial contains no preservative and is suitable for **single use only.**

Aflibercept is formulated as a sterile solution in a single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution for intravitreal injection.

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

4.3.2 Dosage, Administration, and Storage

a. Dosage

Ranibizumab 0.3mg and Aflibercept 2mg

b. Administration

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

c. Storage

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

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

4.4 CONCOMITANT AND EXCLUDED THERAPIES

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

4.5 STUDY ASSESSMENTS

4.5.1 Assessments during the Treatment Period

Patient will be evaluated in the clinic within 1-2 days and 5-7 days post injections. Each clinic visit will include slit lamp examination, indirect ophthalmoscopy, measurements of BCVA, intraocular pressure, ocular inflammation evaluation and pain evaluation using a standard pain scale.

4.5.2 Early Termination Assessments

Subjects who withdraw from the study prior to completion should return for an early termination evaluation **1** day (±**1** days) following the injection for monitoring of all adverse events (serious and nonserious). The schedule of assessments for early termination is the same as that for the final visit.

4.6 SUBJECT DISCONTINUATION

A subject will be withdrawn from the study if he/she is enable to follow-up in the clinic per study protocol. If a subject decides to withdraw from the study, he/she will be scheduled for a follow up visit in 1 month as done routinely with neovascular macular degeneration patients.

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 Sierra Eye Associates or Arshad Khanani M.D. may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

If a subject discontinues from the study, he or she will not be allowed to re-enter the study.

Reasons for subject discontinuation may include, but are not limited to, the following:

- Sensory rhegmatogenous retinal detachment or Stage 3 or 4 macular hole
- Investigator determination that it is not in the best interest of the subject to continue participation
- Pregnancy
- Need for therapy other than ranibizumab or aflibercept
- 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 Sierra Eye Associates or Genentech at any time. Reasons for terminating the study may include the following:

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

4.8 STATISTICAL METHODS

4.8.1 Analysis of the Conduct of the Study

100 subjects will be enrolled in this study

4.8.2 Safety Analyses

Any adverse events, ocular examinations and measurements from all **100** subjects

will be reported. We will be evaluating patients 1-2 days (Visit 1) and again at 5-7 days (Visit 2) post injection and reporting intraocular inflammation (defined as anterior chamber and/or vitreous cells) and pain (as measured on a standardized pain scale) and comparing them to baseline measurements.

4.8.3 Efficacy Analyses

Comparative analysis will be performed to evaluate for post injection pain and inflammation post aflibercept vs. ranibizumab injections.

a. Primary Endpoint

Intraocular inflammation (defined as anterior chamber cells and flare or vitreous inflammation) will be evaluated at baseline, visit #1 and visit #2. Percentages of inflammation (present vs. absent) will be evaluated for each time point by treatment arm using a Chi-square test. Change in inflammation from baseline to visit #1 and baseline to visit #2 will be categorized as worse, same or better. Differences in change in inflammation between treatment arms will be evaluated using a Chi-square test.

a. Secondary Endpoints

· Pain (as measured on a standardized pain scale) will be evaluated at baseline, visit #1 and visit #2. Pain at each time point will be compared between treatment arms using a Student's t-test. Mean change in pain levels from baseline to visit #1 and baseline to visit #2 will be calculated for each treatment arm. Student's t-tests will be used to compare the mean change in pain between treatment arms.**4.8.4 Missing Data**

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

4.8.5 Interim Analyses

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

4.9 DATA QUALITY ASSURANCE

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

5. ASSESSMENT OF SAFETY

Specification of Safety Variables

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

5.1 ADVERSE EVENTS

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with Diabetic Macular Edema that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

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

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

5.2 SERIOUS ADVERSE EVENTS

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

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.

- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

5.3 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

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

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 7 days following the administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

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

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

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the Ranibizumab or Aflibercept, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the Ranibizumab or Aflibercept; and/or the AE abates or resolves upon discontinuation of the Ranibizumab or Aflibercept or dose reduction and, if applicable, reappears upon re-challenge.

No

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

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

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

5.4 EVALUATIONS

Reviews of body systems will be performed. A masked physician will be evaluating anterior chamber and vitreous inflammation using a slit lamp.. Anterior and vitreous inflammation will be graded using the standardized grading systems in Appendix D.

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

5.5 VITAL SIGNS

Will not be measured

5.6 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

5.6.1 Eliciting Adverse Events

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

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

5.6.2 Specific Instructions for Recording Adverse Events

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

a. Diagnosis vs. Signs and Symptoms

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

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is

unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

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

d. Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

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

e. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 30 days after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the {study drug} should be reported as an SAE.

f. Post-Study Adverse Events

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

g. Reconciliation

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

h. AEs of Special Interest (AESIs)

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

The Lucentis Events of Special Interest are:

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

i. SAE Reporting

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682
OR
(650) 225-5288

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to the Ranibizumab or Aflibercept and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the Ranibizumab or Aflibercept will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

Additional Reporting Requirements to Genentech include the following:

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

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

5.6.3 MedWatch 3500A Reporting Guidelines

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

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

5.6.4 Follow-up Information

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

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

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/medwatch/getforms.html

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5.6.6 SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

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

Alternate Fax No: (650) 225-5288

Genentech Study Number	ML29634
Principal Investigator	Arshad Khanani M.D.
Site Name	Sierra Eye Associates
Reporter name	
Reporter Telephone #	
Reporter Fax #	

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

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

6.0 INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study, the following documents must be on file with Sierra Eye Associates or its appointed representative:

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

6.2 STUDY COMPLETION

The following data and materials are required by Sierra Eye Associates before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period (if applicable)

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

6.3 INFORMED CONSENT

Informed consent documents will be provided to each subject.

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

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

The following basic elements must be included:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures or drug used for purposes which are experimental
- A description of any reasonably foreseeable risks or discomforts to the patients
- A description of any benefits to the patient or to others which may reasonably be expected from the research. A description that there may be no benefit from this research.

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality records identifying the patient will be maintained and that notes the possibility that the FDA and the Sierra Eye Associates 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 Sierra Eye Associates (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.5 CASE REPORT FORMS

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

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

6.6 STUDY DRUG ACCOUNTABILITY

The Investigator is responsible for the control and distribution of study drug.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure.

6.7 DISCLOSURE OF DATA

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

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

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

6.8 RETENTION OF RECORDS

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

6.9 STUDY CLOSE-OUT

The Clinical Study Report (final study report) will be emailed to lucentisgsr_coa-d@gene.com or faxed to 866-728-4622 . Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned contact for the study.

REFERENCES

1. Khanani et al**.** Evaluation of Intraocular Inflammation and Pain Post Intravitreal Injection of Ranibizumab or Aflibercept: The PLANET Study. Presented at ASRS 2014. San Diego, CA.
2. Hahn P et al. Aflibercept-related sterile inflammation. Ophthalmology. 2013 May;120(5):1100-101
3. Goldberg RA et al. Noninfectious Inflammation After Intravitreal Injection of Aflibercept: Clinical Characteristics and Visual Outcomes. Am J Ophthalmol. 2014 Jun 28
4. Kiss et al. The Pattern of Anti-VEGF Use in Neovascular Age- Related Macular Degeneration and Diabetic Macular Edema: A US Claims Analysis. Presented at ASRS 2014, San Diego, CA.
5. Fine et al. Frequency and Management of Intraocular Inflammation after Aflibercept injection. Presented at ASRS 2014, San Diego, CA.
6. Jabs, DA et al. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-16.

APPENDIX A
Study Flowchart

Procedure	Day 0	Visit 1 (24-48 hours post Day 0)	Visit 2 (5-7 Days post Day 0)
Informed Consent	X		
Randomization	X		
Demographic Data	X		
Medical and Ophthalmic history (including specifics on ophthalmic history, any previous injections with agent and month/year, and any prior surgeries within past two years.)	X		
Slit lamp exam and OCT	X	X	X
Indirect ophthalmoscopy exam	X	X	X
Treatment Assignment	X		
BCVA and Intraocular pressure	X	X	X
Ranibizumab or Aflibercept treatment[b]	X		
Ocular Inflammation Evaluation	X	X	X
Pain Evaluation	X	X	X
AE / SAE monitoring		X	X

APPENDIX B
Pre-Injection Procedures for All Subjects

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

The following procedures (except where noted) will be conducted by the investigator.

- The technician assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4×4 sterile pads, pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, 0.5% proparacaine hydrochloride, 5% povidone iodine ophthalmic solution, 1% lidocaine for injection, and injection supplies.
- Instill 2 drops of 0.5% proparacaine hydrochloride 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. Make certain that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.
- The investigator will glove, and place the speculum underneath the eyelid of the study eye.
- Instill 2 drops of 5% povidone iodine ophthalmic solution in the study eye, making sure the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.
- Saturate a sterile cotton-tipped applicator with 0.5% proparacaine hydrochloride drops and hold the swab against the planned intravitreal injection site for 10 seconds in preparation for the subconjunctival injection of 1% lidocaine hydrochloride ophthalmic solution for injection (without epinephrine).
- Use a sterile 4×4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.
- ***Instruct subject to direct gaze away from syringe prior to ranibizumab or aflibercept injection.***

APPENDIX C

Analysis of Similar Events Template for IND Safety Reports

IND Safety Report

Case Summary

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

PREVIOUS REPORTS

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

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

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, Sierra Eye Associates believes there is a reasonable possibility of a cause-and-effect relationship between administration of _____(insert study drug name) and the occurrence of _____(insert AE).

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

Or

Based on review of available data, the **Sierra Eye Associates** does not believe that there is a reasonable possibility of a cause-and-effect relationship between administration of _____(insert study drug name) and the occurrence of _____(insert AE).

Explain if warranted. Do not speculate.

Or

Based on review of available data, the **Sierra Eye Associates** cannot establish or exclude the possibility of a cause-and-effect relationship between administration of _____(insert study drug name) and the occurrence of _____(insert AE).

Explain if warranted. Do not speculate.

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

APPENDIX D

Anterior Chamber Cell

Grade 0	<1 cells
Grade 0.5+	1-5 cells
1+	6-15 cells
2+	16-25 cells
3+	26-50 cells
4+	>50 cells

Anterior Chamber Flare

0	No flare
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrous or plastic aqueous)

Vitreous Cell Grade

0	No haze

0.5	Trace - Slight blurring of Optic Nerve (ON) border
1+	Slightly blurry ON plus margins
2+	Moderately blurred ON plus vessels
3+	ON border blurry, just visible
4+	ON obscured

APPENDIX E

NUMERICAL RATING SCALE FOR PAIN

An 11 point numerical rating scale from 0-10 will be administered to each patient verbally. Patients are asked to verbally rate their pain "on a scale from 0 to 10, with 0 equal to no pain and 10 equal to worst possible pain." Each patient will be read the following script, with no deviations:

"I am going to ask you to rate the level of pain you felt from your injection on a scale from 0 to 10. A rating of zero means you experienced no pain at all. Ratings from 1-3 designate mild levels of pain. Ratings from 4-6 designate moderate levels of pain. Ratings from 7-9 designate severe levels of pain. A rating of 10 designates the worst possible pain. Please tell me, on this scale from 0-10, what level of pain you felt from your injection?"