EAGLE: Evaluating Genotypes Using Intravitreal Aflibercept Injection
NCT: 02689518
Document Date: February 21, 2019

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Version date: February 7, 2018 (Version 6.0)

1. PROJECT TITLE

EAGLE: Evaluating Genotypes Using Intravitreal Aflibercept Injection

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

University of California, San Diego
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Biomedical Research Facility 2
Osler Lane #4186, La Jolla, CA 92093

Retina Consultants San Diego
12630 Monte Vista Road, Suite#104
Poway, CA 92064

4. ESTIMATED DURATION OF THE STUDY

12 months is the study duration. From start of recruitment to last subject's final visit is estimated to be approximately 4 years (approximately 3 years to recruit, 1 year duration, last subject to end 1 year later estimated December 2017).

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

The purpose of this study is to determine if known elements of an individual's genetic makeup has any effect on his or her individual anatomical response to Eylea® (aflibercept). In addition to characterizing the subject's response using measurements of central retinal thickness and presence of retinal fluid (as measured by optical coherence tomography), we will also be comparing individual visual acuity, presence of angiographic lesions, and number of injections accrued over the 12 months of participation.

6. SPECIFIC AIMS

This project will provide important information on inherent VEGF risk and the likelihood of intravitreal aflibercept injection treatment efficacy for AMD patients. This project will also be signal seeking to see if different genetic polymorphisms correlate with treatment outcomes.

Primary Endpoints

Correlation of CFH, HTRA1, VEGFA, C3, TIMP3, APOE, CETP, LIPC, TGFBR1, CFI, and CFB allele frequencies and VEGFA expression in lymphoblastoid cell lines with response to intravitreal aflibercept injection treatment, based on anatomic outcomes:

- Early response (at Month 3; on SD-OCT) as compared to outcomes collected at the Screening Visit-
    - Reduction in central retinal thickness by $\geq$ 50%, OR

- Central retinal thickness < 300um, OR
- Absence of retinal fluid

- Later response (at Month 12; on SD-OCT) as compared to outcomes collected at the Screening Visit -
  - Reduction in central retinal thickness by ≥ 50%, OR
  - Central retinal thickness < 300um, OR
  - Absence of retinal fluid
- Poor response, defined as no reduction of fluid, or central retinal thickness at Month 12 as compared to outcomes collected at the Screening Visit

Secondary Endpoints

Correlation of CFH, VEGF and HTRA1, CFH, HTRA1, VEGFA, C3, TIMP3, APOE, CETP, LIPC, TGFBR1, CFI, and CFB allele frequencies:

- With visual outcomes as compared to outcomes collected at the Screening Visit –
  - Early response, defined as gain ≥ 0 letters at Month 3
  - Later response, defined as gain ≥ 0 letters at Month 12
  - Poor response, defined as loss of visual acuity (gain < 0 letters) at Month 12
- With change in angiographic characteristics on fluorescein angiography and/or OCT (lesion size, lesion type, etc) as compared to outcomes collected at the Screening Visit
- With number of injections through Month 12
  - Mean number of intravitreal aflibercept injection injections required through Month 12 will be calculated for the overall group, and separately by response group (early, later, and no response to treatment).

Safety evaluation

Incidence and severity of ocular and non-ocular adverse events will be evaluated.

7. BACKGROUND AND SIGNIFICANCE

Age-related macular degeneration (AMD) is a progressive disease that causes irreversible visual impairment and blindness in nearly 50 million people globally. Current estimates of patients affected with AMD are higher than those affected by Alzheimer's disease. Although geographic atrophy and neovascularization represent the advanced forms of AMD, neovascular AMD is the more aggressive form and accounts for almost 90% of blindness from this disease. It is characterized by choroidal neovascularization (CNV), which is the development of abnormal blood vessels underneath the retina. Recent randomized clinical trials (VIEW 1, VIEW 2) have conclusively demonstrated that continued intravitreal therapy with Intravitreal aflibercept injection in patients with subfoveal CNV from AMD leads to stabilization of vision in over 90% of patients and improvement in vision in at least a third of the patients and has led to the approval of Intravitreal aflibercept injection (2.0 mg) for the treatment of neovascular AMD. Both Intravitreal aflibercept injection treatment arms (Intravitreal aflibercept injection 2 mg administered every 8 weeks following 3 initial monthly doses, or Q 4 weeks following 3 initial monthly doses) were shown to have efficacy that was clinically equivalent to existing therapy[1].

Vascular endothelial growth factor (VEGF)'s mRNA and protein levels are elevated in individuals with the neovascular form of ocular diseases such as diabetic retinopathy and AMD. Despite empirical success in treating wet AMD patients with anti-VEGF drugs, the basic pathogenic mechanisms remain largely unknown. VEGFA gene serves as a good candidate for testing pharmacogenetic relationships between genotypes and therapy outcomes. VEGFA has been reported as a

predisposing gene to AMD [2-4], yet there have been few studies investigating the association between VEGFA genotypes and response to anti-VEGF therapy. A recent meta-analysis investigating the genetic susceptibility of AMD demonstrated that VEGFA-rs943080 is in strong linkage disequilibrium (LD) with rs4711751 (r2 = 1.0 in 1000 Genomes CEU data), which is significantly associated with advanced AMD ([OR=1.15 (95% CI: 1.10-1.21), P = 8.7x10-9])[3]. In preliminary work, we investigated whether there is an association between the response to anti-VEGF treatment for neovascular AMD and the VEGFA gene, clinical characteristics, demographic factors, or comorbidities. We described a significant association between response to anti-VEGF therapy and the VEGFA-rs943080 variant. For the rs943080 polymorphism, the poor-responder group had a higher frequency of the T allele and TT genotype than the responder group. Lymphocyte cells with the VEGFA rs943080 TT genotype had a higher VEGFA expression than cells with the VEGFA rs943080 CC genotype, suggesting that VEGFA expression is associated with response to anti-VEGF therapy in neovascular AMD (6). Additionally, we have recently demonstrated that nucleotide polymorphisms (SNP) and a haplotype in region of HTRA1 is a major risk factor for neovascular AMD. The HTRA1 gene encodes a secreted serine protease. Our study indicates a key role for HTRA1 in AMD susceptibility, and identifies a new pathway for neovascular AMD pathogenesis[5]. We will investigate the efficacy of Intravitreal aflibercept injection therapy relative to CFH, HTRA1, VEGFA, C3, TIMP3, APOE, CETP, LIPC, TGFBR1, CFI, and CFB and other AMD candidate gene status.

Patient response to intravitreal aflibercept injection treatment is heterogeneous and currently not well understood. Recent data by several independent laboratories suggest that genetic polymorphisms affecting VEGF activity or expression may contribute to wet AMD pathogenesis. This will likely contribute to heterogeneity in anti-VEGF treatment responses. HTRA1 has also been recently demonstrated to play an important role in neovascular AMD and is expressed in retinal vasculature as well. The goal of our study is to identify genetics determinants of anti-VEGF response.

8. PROGRESS REPORT

Not available at this time.

9. RESEARCH DESIGN AND METHODS

This is a phase IV, multicenter, open-label study of 100 treatment-naïve (study eye only) neovascular wet-AMD patients treated on-label with intravitreally administered aflibercept injection. Their blood will be genotyped and sequenced for various SNPs on VEGF and HTRA1 and other AMD candidate genes.

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
	D 0	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12/ Early Term
		±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Informed Consent	X												
Initial Medical and Ocular History	X												

Demographic Data	X												
ETDRS BCVA	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit Lamp Exam inc IOP	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated Fundus Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X	X	X
Fluorescein angiography	X												
Blood draw	X[1]												
Intravitreal Injection	X	X	X	X[2]	X	X[2]	X	X[2]	X	X[2]	X	X[2]	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedures and assessments

At baseline and all monthly visits:

- Manifest refraction and best corrected visual acuity test using 4m ETDRS chart and standard trial lenses [3]
- Intraocular pressure test using Goldmann's Applanation Tonometry or Tono-pen™
- Optical coherence tomography
- Dilated binocular indirect high magnification ophthalmoscopy
- Slit lamp examination

At baseline only:

- Fluorescein angiography

Treatment

Intravitreal aflibercept injection 2 mg (0.05 mL) will be administered every 4 weeks for the first 3 months, followed by 2 mg (0.05 mL) intravitreal injections once every 8 weeks (2 months) with the option to treat monthly based on retreatment criteria for a total duration of 12 months.

10. HUMAN SUBJECTS

Approximately 100 treatment- naïve wet-AMD patients will be recruited across the study sites.

Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Age ≥ 50 years
2. Naïve neovascular wet-AMD
3. Willing and able to comply with clinic visits and study-related procedures
4. Provide signed informed consent

Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

[1] May be performed once, at any point during study participation.

[2] Per pre-defined criteria as outlined by study protocol.

[3] If manifest refraction and best corrected visual acuity test using 4m ETRS chart and standard trial lenses is not conducted during the Screening Visit, best corrected visual acuity measurement from the most recent clinical visit after diagnosis of neovascular-AMD may be used.

1. Previous therapy in study eye for AMD or other retinal disease which may be used in the treatment of AMD
2. Previous subfoveal focal laser photocoagulation involving the foveal center in the study eye
3. History of vitrectomy, submacular surgery, or other surgical intervention for AMD in the study eye
4. Any concurrent intraocular condition in the study eye (e.g. diabetic retinopathy or glaucoma) that, in the opinion of the investigator, could either
   - 4.1 Require medical or surgical intervention during the study period to prevent or treat visual loss that might result from that condition, or
   - 4.2 If allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the study period
5. Active intraocular inflammation (grade trace or above) in the study eye, or history of idiopathic or autoimmune-associated uveitis in either eye
6. Current vitreous hemorrhage in the study eye
7. History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4) in the study eye
8. Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
9. Aphakia, ACIOL, or unstable PCIOL
10. Uncontrolled glaucoma in the study eye (defined as intraocular pressure ≥30 mmHg despite treatment with anti-glaucoma medication)
11. Pregnant or breast-feeding women
12. Sexually active men[4] or women of childbearing potential[5] who are unwilling to practice adequate contraception during the study (adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly)
13. Any other condition that the investigator believes would pose a significant hazard to the patient if the investigational therapy were initiated

*Contraception is not required for men with documented vasectomy.
Postmenopausal women must be amenorrheic for at least 12 months in order **not to be considered of child bearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Potential subjects will be identified through their routine appointments at the Shiley Eye Institute and at the VASDHS, at which the physicians also hold clinical privilege. They will be invited to participate by their physician during their appointment.

Potential subjects will be identified through the same manner at the subsites participation in this study.

12. INFORMED CONSENT

A study consent form along with the HIPAA authorization that will be used is submitted with this application.

Informed consent for the study proposed here will be obtained prior to subject participation by trained study coordinators. The subject will be given an opportunity to read the consent form and to have

[4] Contraception is not required for men with documented vasectomy.
[5] Postmenopausal women must be amenorrheic for at least 12 months in order **not** to be considered of child-bearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

their questions answered. The study and all its elements will be carefully described to the potential subject. The subject is asked if he/she assents to the study. Informed consent will be documented by the signatures of the subject, and the subject will receive a copy of the signed consent, the HIPAA authorization, and of the Human Subjects' Bill of Rights.

If the subject dissents, all potential participation is void.

13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative to participating in the study is to not participate in this study.

14. POTENTIAL RISKS

Eye Examination

The risks of the eye examination are no different than they would be on a routine visit to the ophthalmologist. The drops used to dilate the pupils may sting temporarily and cause blurry vision, increased light sensitivity and glare in bright light, allergic reaction, and may in rare instances, cause a type of glaucoma for which prompt treatment is needed. The pupils may remain dilated for 4-6 hours.

Intravitreal Injection

The risks of receiving Eylea® treatment or eye exams during this study are no different than they would be if prescribed outside the study. The safety and tolerability of intravitreal Eylea® injections have been investigated in previous Phase I, I/II, III, and IIIb studies in AMD. Potential safety issues associated with the route of administration or the pharmacology of Eylea® in the study population include decreased BCVA, pain at the injection site, intraocular inflammation, intraocular infection, transient and/or sustained elevation of intraocular pressure (IOP), cataract development or progression, retinal or intravitreal hemorrhage, macular edema, retinal break or detachment, and arterial thromboembolic events (ATEs). Adverse events that should be considered ATEs include, but are not limited to, myocardial infarction and cerebrovascular accident (ischemic and hemorrhagic).

Blood Draw and Fluorescein Angiography

The blood draw may cause slight discomfort and may result in a temporary bruise at the needle site, and rarely the possibility of infection. Also, subjects may faint in response to blood draw. The same risks apply to fluorescein angiography, in which a dye is injected into a patient's vein. The most common side effects of this dye are nausea and vomiting; however, occasional allergic reactions and fainting may occur. A severe allergic reaction would require immediate medical treatment and could result in permanent disability or death. Patients will be carefully observed during this procedure to minimize the risk to patient health.

Confidentiality

There is also the potential risk of loss of patient confidentiality. It is conceivable that patients may be placed at a disadvantage if employers or potential insurers gain access to genetic or other health information. Many precautions will be taken to protect this information.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Blood Draw

Blood will be drawn by trained study personnel.

Intravitreal Injection

In order to safely monitor these risks, the following procedures will be followed: Following each intravitreal injection of Eylea®, a finger counting test will be performed for each patient after each injection by the physician; hand motion and light perception will be tested when necessary. IOP will be measured 15-30 minutes after each injection. If post-injection IOP increases ≥ 10 mmHg compared with the pre-injection measurement, then the IOP measurement will be performed again at 60 (±10) minutes. If there are no safety concerns up to 60 (±10) minutes following an injection, patients will be allowed to leave the clinic. If any safety concern or immediate toxicity is noted, the patient will remain at the clinic and will be treated according to the designated physician's clinical judgment. 2-7 days after each study drug treatment, the patient will be contacted by telephone by study staff and asked whether or not any eye pain, unusual redness, a decrease in vision, or other new eye problems have occurred. If any of these symptoms have occurred, the study ophthalmologist may decide that the patient should come to the clinic for additional eye examinations and treatment, if necessary.

Study drug administration will be held at the investigator's discretion if he or she suspects any safety or other issues. If the investigator decides to hold a dose, the reason will be recorded on the source documents. In the event a subject experiences an adverse event in the study eye that is considered by the investigator to be severe in intensity or serious in nature, consideration should be given to holding treatment or discontinuing the patient from study treatment. This decision will be at the investigator's discretion and should be recorded on the source documents.

Early Withdrawal

Patients withdrawn from the study prior to completion will be asked to return for an early termination evaluation 30 days (± 7 days) following their last injection for monitoring of all adverse events (serious and non-serious; ocular and non-ocular) as well as for final study visit assessments.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Patients are evaluated in a private room in regular clinic. Access to the patient is limited by the study physician. In order to maintain subject privacy, all study personnel will not share information with patients about their care or progress unless they are in a private, secure area. Patient information in paper form is kept in locked filing cabinets. All electronic information is kept on password-protected computers. Patient identifiers are removed and arbitrary numbers are assigned to materials that are shared with sources involved in the study. In order to maintain patient confidentiality any person who has access to or maintains patient records will ensure that confidentiality will be maintained at all times by keeping all records under their control or in locked cabinets. All study staff are HIPAA trained.

17. POTENTIAL BENEFITS

This study primarily benefit researchers and the field of Ophthalmology with a better understanding of AMD pathogenesis. Patients who participate in the study will receive ophthalmological care and an investigational drug, which may or may not result in a benefit to their ocular health.

18. RISK/BENEFIT RATIO

The risks of receiving Eylea® treatment during this study are no different than they would be if your doctor prescribed it for you outside the study. Soreness or bruising at the site of needle insertion may occur at the needle site, and rarely the possibility of infection.

19. EXPENSE TO PARTICIPANT

This study will not involve any expense to the participant.

20. COMPENSATION FOR PARTICIPATION

This study will not involve any compensation for the participant.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

All clinical procedures will be performed by Shiley Eye Institute physicians (Drs. Goldbaum, Zhang and Ferreyra) and research/clinic staff who are licensed or certified to perform their applicable tasks (including visual acuity examiners and photographers). Administrative tasks, blood draws and many other research-related tests will be performed by the trained research coordinators.

At the subsite: Dr. Tornambe has a current medical license and privilege at his respective institution.

Cindy Wen and Megan Lyons will be the study coordinators, at the Shiley Eye Institute with technical and administrative roles.

22. BIBLIOGRAPHY

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23. FUNDING SUPPORT FOR THIS STUDY

This is an investigator-initiated trial funded by Regeneron Pharmaceuticals, Inc. through UCSD Office of Contracts and Grants Administration (OCGA).

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

See attached investigational drug fact sheet and investigator brochure for study drug aflibercept.

26. IMPACT ON STAFF

The research staff, including the study coordinators, will perform the majority of tasks involved in clinical visits. Ophthalmic technicians may assist with certain procedures, but not to the extent that regular clinics will be inconvenienced or delayed in any way.

27. CONFLICT OF INTEREST

Conflict of interest forms have been submitted to the clinical trials office. Neither Dr. Goldbaum nor the co-investigators have financial relationships with the sponsor.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

No surrogate consent will be sought for this study.

Version date: May 11, 2011