Clinical Study Protocol

A Prospective, Single-Blind, Randomized Study to Evaluate Intravitreal Aflibercept Injection (IAI) versus Sham as PROphylaxis against CONversion to Neovascular Age-Related Macular Degeneration (AMD) in High-Risk Eyes

Compound:	Intravitreal Aflibercept Injection 2 mg
Study Name:	IAI versus Sham as Prophylaxis against Conversion to Neovascular AMD (PRO-CON)
Clinical Phase:	II
Study Number:	VGFTe-AMD-1507
Version & Date of Issue:	3.0 dated 24-NOV-2015
Primary Investigator:	Jeffrey S. Heier, MD

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE:	A Prospective, Single-Blind, Randomized Study to Evaluate Intravitreal Aflibercept Injection (IAI) versus Sham as Prophylaxis against Conversion to Neovascular Age-Related Macular Degeneration (AMD) in High-Risk Eyes
TITLE IN LAY TERMS:	IAI as Prophylaxis against Conversion to Neovascular AMD (PRO-CON)
SITE LOCATION(S)	Ophthalmic Consultants of Boston, Boston, MA New Jersey Retina, NJ Retina-Vitreous Associates Medical Group, Los Angeles, CA Retina Consultants of Houston, Houston, TX
OBJECTIVE(S):	To evaluate IAI 2mg as prophylaxis against the conversion to neovascular age-related macular degeneration (AMD) in high-risk eyes.
STUDY DESIGN:	Multicenter, prospective, active-controlled, single-blind study involving 128 subjects randomized 1:1 to receive IAI every three months for 24 months versus sham injections.
STUDY DURATION:	18-month enrollment period, then 24-month treatment period
ESTIMATED STUDY COMPLETION DATE:	September 2018
POPULATION	128 enrolled subjects with high-risk non-neovascular AMD in one eye (study eye) defined as having: • Intermediate AMD in the study eye, defined as the presence of greater than ten intermediate sized drusen (≥ 63 and <125 μm), 1 or more large druse (≥125 μm), and/or retinal pigmentary changes. and • Neovascular AMD in the fellow eye
TREATMENT(S)	
Study Drug:	Intravitreal aflibercept injection
Dose/Route/Schedule:	2 mg / intravitreal injection / Q3-month for 24 months
Placebo:	Sham injection
Dose/Route/Schedule:	Q3-month for 24 months

ENDPOINT(S)

Primary:

Proportion of subjects converting to neovascular AMD at 24 months, characterized by the development of choroidal neovascularization (CNV). The development of CNV will be assessed by:

- CNV leakage on FA, and
- Evidence of any fluid on SD-OCT.

Conversion will be confirmed by the reading center ("confirmed conversion"). The Kaplan-Meier method will be used to estimate time to conversion using the conversion criterion**,** and the log-rank test will be used to compare the time course among treatment groups.

Secondary:

- Mean change in visual acuity at 24 months compared to baseline
- Percentage of subjects losing < 15 ETDRS letters at 24 months as compared to baseline
- Incidence and severity of potential ocular side effects including endophthalmitis, retinal detachment, cataract, and intraocular inflammation
- Incidence and severity of systemic side effects
- Development/progression of geographic atrophy.

Interim:

An interim analysis will be performed at Month 12.

Exploratory Analyses:

In subjects who choose to participate in the genomics sub-study, blood samples will be taken for exploratory DNA analysis.

In subjects who convert to neovascular AMD, additional analyses include:

- Mean change in visual acuity at conversion
- Mean change in visual acuity at 24 months
- Mean number of IAI injections through 24 months.
- Mean size of choroidal neovascular membrane at 24 months per FA
- Detection of conversion to neovascular AMD by OCT angiography
- Correlation of CNV detection by OCT angiography relative to FA
- Timing of CNV detection by OCT angiography relative to FA

In subjects who choose to participate in the home monitoring sub-study, exploratory analyses include the correlation between an alert generated by Paxos Checkup™ application ("app") and a confirmed conversion at subject's next office visit.

PROCEDURES AND ASSESSMENTS:	Enrolled subjects will be evaluated at Baseline and every three months thereafter for a 24-month study period. Assessments at each visit include: • Manifest refraction and ETDRS visual acuity testing • Slit lamp exam and dilated fundus exam • Spectral-domain optical coherence tomography (SD-OCT) using Avanti device • OCT angiography using Avanti AngioVue™ • Fluorescein angiography (FA) Fundus photography will also be performed at Baseline, Month 12 and Month 24 visits. Required assessments at a Suspected Conversion Visit (SCV, see Section 6.2.5) include: • Manifest refraction and ETDRS visual acuity testing • Slit lamp exam and dilated fundus exam • Spectral-domain optical coherence tomography (SD-OCT) using Avanti device; • OCT angiography using Avanti AngioVue™ And, per investigator's discretion: • FA (required if investigator believes conversion has occurred) • Fundus photography. At any time during the 24-month study period, in the event of conversion of the study eye to neovascular AMD, the investigator will treat subject with IAI at a frequency per his/her discretion. Subjects participating in the genomics sub-study will have a blood sample taken upon enrollment into the main study. Subjects participating in the home monitoring sub-study will be trained to use the Paxos Checkup™ app on a personal wireless device to perform at-home testing at least twice per week including the Visual Acuity and Amsler Grid tests within the app.
STATISTICAL PLAN	The Kaplan-Meier method will be used to estimate time to conversion using the conversion criterion, and the log-rank test will be used to compare the time course among treatment groups

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1.0 INTRODUCTION AND RATIONALE

1.1 Introduction

Age-related macular degeneration (AMD) has surpassed cataract as the leading cause of visual impairment in the developed world, accounting for more than 50% of all blindness in the United States[1]. According to a 2004 study by the Eye Diseases Prevalence Research Group, 8 million Americans had bilateral intermediate dry AMD and 2 million had advanced AMD, defined as neovascularization or geographic atrophy[2]. Although dry AMD is significantly more prevalent, neovascular AMD continues to account for more than 90% of significant visual loss[3].

1.2 Rationale

There has been extensive research evaluating risk factors and conversion rates related to the transformation from advanced dry AMD to neovascular AMD, an event that can lead to precipitous vision loss without prompt treatment. Risk factors that have been found to be statistically significant include age, gender, race, and smoking[4]. Over a mean follow-up time of 6.3 years, The Age-Related Eye Disease Study (AREDS) reported a 10% conversion rate in at least one eye of patients with bilateral drusen without advanced AMD. When they looked at fellow eyes of patients with unilateral neovascular AMD, the rate went up to 35% over a mean follow-up time of 6.3 years[5]. With the advent of the anti-VEGF treatment era, patients with unilateral neovascular AMD have been studied closer and varying conversion rates have been reported from 5 to 20% per year of follow-up[6]. One study included evidence of neovascularization by SD-OCT (e.g. subretinal fluid) in addition to fluorescein angiographic findings and reported conversion rates as high as 60% per year[6].

Although there has been a tremendous effort to establish treatment prevention for this subset of patients, high-dose vitamins and antioxidants based on the AREDS has been the only proven treatment with a modest reduction in risk of 25% over 5 years[7]. With the overwhelming success of anti-VEGF agents in neovascular AMD, researchers have asked whether anti-VEGF agents can affect the natural course of high-risk dry AMD. Barbazetto and associates reviewed the fellow eyes of patients enrolled in MARINA and ANCHOR studies and found that conversion rates in fellow eyes among treatment cohorts (receiving monthly ranibizumab in the study eye) was not statistically different from the conversion rates among their respective non-treatment cohorts

(sham injection in MARINA and photodynamic therapy in ANCHOR). Their conversion rates to neovascular AMD in fellow eyes, which were based on fluorescein angiography readings, were 21-26% over 12 months and 35-39% over 24 months[5]. They concluded that the fractional serum anti-VEGF concentrations achieved after intravitreal injection in the treatment eye did not have an effect on the conversion rate of the fellow eye.

With such significant conversion rates among patients who have unilateral neovascular AMD, the next logical question would be whether direct intravitreal anti-VEGF in eyes with high-risk dry AMD would provide a prophylactic effect against the conversion to neovascular AMD. Such a prophylactic effect could be extremely valuable because of its impact on vision preservation and quality of life, especially to patients who already suffer visual impairment in one eye.

1.2.1 Rationale for Study Design

Neovascularization in AMD is highly dependent on the presence of elevated levels of free VEGF. Inhibition of free VEGF with aflibercept may influence the rate of developing choroidal neovascularization.

1.2.2 Rationale for Dose Selection

The 2 mg aflibercept dose was chosen as its safety profile has been established in previous clinical studies with IVT aflibercept.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate IAI 2 mg as prophylaxis against the conversion to neovascular age-related macular degeneration (AMD) in high-risk eyes at 24 months.

2.2 Secondary Objectives

The secondary objectives of the study are to evaluate:

- Mean change in visual acuity at 24 months compared to baseline

- Percentage of subjects losing < 15 ETDRS letters at 24 months and change in visual acuity from baseline;
- Incidence and severity of potential ocular side effects of endophthalmitis, retinal detachment, cataract, and intraocular inflammation
- Incidence and severity of systemic side effects; and
- Development/progression of geographic atrophy.

2.3 Exploratory Objectives

Additional exploratory analysis will include:

- In subjects who choose to participate in the genomics sub-study, blood samples will be taken for exploratory DNA analysis.
- In subjects who convert to neovascular AMD, additional analyses include:
    - Mean change in visual acuity at conversion
    - Mean change in visual acuity at 24 months
    - Mean number of IAI injections through 24 months
    - Mean size of choroidal neovascular membrane at 24 months per FA
    - Detection of conversion to neovascular AMD by OCT angiography
    - Correlation of CNV detection by OCT angiography relative to FA
    - Timing of CNV detection by OCT angiography relative to FA
- In subjects who choose to participate in the home monitoring sub-study, exploratory analyses include the correlation between an alert generated by the Paxos Checkup™ application ("app") and a confirmed conversion at subject's next office visit.

3. STUDY DESIGN

3.1 Study Description and Duration

This is a prospective, single-blind, randomized study to evaluate intravitreal aflibercept injection (IAI) versus sham as prophylaxis against conversion to neovascular age-related macular degeneration (AMD) in "high-risk" subjects. High risk is defined as having intermediate AMD in one eye (study eye), defined as the presence of greater than ten intermediate sized drusen (≥ 63

and <125 μm), 1 or more large druse (≥125 μm), and/or retinal pigmentary changes **and** neovascular AMD in the fellow eye.

128 subjects will be enrolled in the trial and randomized in a 1:1 ratio to receive either IAI every three months for 24 months or sham injections. Enrollment will be stratified in order to ensure a balance between the two treatment groups for subjects who were diagnosed with exudative AMD within the past two years versus those diagnosed more than two years prior to Baseline.

Study assessments will be conducted at required visits every three months and include manifest refraction and ETDRS visual acuity testing, slit lamp exam and dilated fundus exam, spectral-domain optical coherence tomography (SD-OCT) using Avanti device, and OCT angiography using Avanti AngioVue™, and fluorescein angiography. Fundus photography will also be performed at Baseline, Month 12 and Month 24 visits.

In the event of conversion to neovascular AMD in the study eye at any point during the study, the investigator will treat the subject with IAI at a frequency per his/her discretion.

In subjects who participate in the genomics sub-study, blood samples will be taken for exploratory DNA analysis.

Subjects participating in the home monitoring sub-study will be trained to use the Paxos Checkup™ app on a personal wireless device to perform at-home testing twice per week including the Visual Acuity and Amsler Grid tests within the app.

3.2 Planned Interim Analysis

Interim analyses will be performed when all subjects have completed Month 12 visits. See Section 9.5.4 for specific analyses.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

4.1 Number of Subjects Planned

128 subjects will be enrolled in a 1:1 ratio: 64 subjects will be randomized to IAI treatment every three months for 24 months and 64 control subjects will receive sham injections every three months for 24 months. Enrollment will be stratified in order to ensure a balance between the two treatment

groups for subjects who were diagnosed with exudative AMD within the past two years versus those diagnosed more than two years prior to Baseline.

4.2 Study Population

Eligible subjects will have high-risk non-neovascular AMD in one eye (study eye) defined as having:

- Intermediate AMD in the study eye, and
- Neovascular AMD in the fellow eye

4.2.1 Inclusion Criteria

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

- Study eye must have a diagnosis of non-exudative age-related degeneration characterized by the presence of greater than ten intermediate sized drusen (≥ 63 and <125 μm), 1 or more large druse (≥125 μm), and/or retinal pigmentary changes.
- Fellow (non-study) eye must have CNV lesion (i.e., leakage on fluorescein angiography and/or subretinal, intraretinal, or sub-RPE fluid on OCT) secondary to age-related macular degeneration OR history of CNV lesion secondary to age-related macular degeneration, as confirmed by current or past treatment or current or past diagnostic imaging.
- Subject must be willing and able to comply with clinic visits and study-related procedures.
- Subject must provide signed informed consent.
- Subject must be able to understand and complete study-related questionnaires.
- In order to participate in the home monitoring sub-study, subjects must have an approved wireless device (i.e. iPhone, iPad, or iPod running iOS 6.0 or later) or be willing to use a loaned device and have access to a wireless Internet connection for the duration of the study.

4.2.2 Exclusion Criteria

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

- Evidence of neovascular AMD in the study eye at time of enrollment or anytime in the past. The reading center must confirm that there is no evidence of neovascular AMD in the study eye prior to enrollment.
- Previous treatment with verteporfin PDT, anti-VEGF therapy, laser, external beam radiation or other AMD therapy in the study eye.
- History of macular hole in study eye.
- History of vitrectomy in study eye.
- Lens extraction or implantation within the last 3 months.
- Capsulotomy within the last 1 month.
- Lens or other media opacity that would preclude good fundus photography or angiography within the next 2 years.
- Macular edema or signs of diabetic retinopathy more severe than 10 microaneurysms or blot hemorrhages.
- Retinal changes related to high myopia and/or myopic correction greater than 8.00 diopters spherical equivalent [sphere + ½ cylinder].
- Any progressive ocular disease that would affect visual acuity within the next 2 years.
- Previous participation in any studies of investigational drugs likely to have ocular effects within 30 days preceding the initial study treatment.
- Concurrent use of systemic anti-VEGF agents.
- Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye.
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.
- For subjects who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye cannot exceed 8 diopters of myopia.
- Uncontrolled glaucoma in the study eye (defined as intraocular pressure > 25 mmHg) despite treatment with anti-glaucoma medication).
- Subjects who are unable to be photographed to document CNV due to known allergy to fluorescein dye, lack of venous access or cataract obscuring the CNV.

- Subjects with other ocular diseases that can compromise the visual acuity of the study eye such as amblyopia and anterior ischemic optic neuropathy.
- Current treatment for active systemic infection.
- Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders.
- History of recurrent significant infections or bacterial infections.
- Inability to comply with study or follow-up procedures.
- Pregnancy (positive pregnancy test) or lactation

  Premenopausal women not using adequate contraception. The following are considered effective means of contraception: surgical sterilization or use of oral contraceptives, barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel, an IUD, or contraceptive hormone implant or patch.
- Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated
- Participation in another simultaneous medical investigation or trial
- Pregnant or breast-feeding women
- Sexually active men* or women of childbearing potential** who are unwilling to practice adequate contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept (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)

*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.

4.3 Premature Withdrawal from the Study

A subject has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator has the right to withdraw a subject from the study in the event of illness, adverse event ("AE"), treatment failure, protocol violation, cure, and for administrative or other reasons. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subjects will be avoided.

Should a subject (or a subject's legally authorized guardian or representative) decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. Early termination procedures will be followed.

4.4 Replacement of Subjects

Subjects prematurely withdrawn from the study can be replaced, if needed, to ensure an adequate number of evaluable subjects. The investigator, in cooperation with the study statistician, will decide whether or not to replace withdrawn subjects.

5. STUDY TREATMENTS

5.1 Investigational Treatment:

IAI 2 mg at baseline and at an interval of every 3 months thereafter for 24 months (total of 8 injections), until/unless conversion occurs.

5.2 Reference Treatment

Observation with sham injections at baseline and at an interval of every 3 months thereafter for 24 months (total of 8 sham injections), until/unless conversion occurs.

5.3 Background Treatment(s)

Many subjects will be currently taking AREDS vitamin supplements and may continue to do so throughout the study.

If a subject is currently receiving therapy in his fellow eye other than IAI, treatment will be switched to IAI. IAI is the only treatment allowed by the study for the treatment of neovascular AMD. Subject may not have received any treatment for exudative AMD in his fellow eye other than IAI within 28 days prior to Day 0.

5.4 Treatment on Conversion

In the event of conversion to neovascular AMD in subject's study eye, the investigator will treat subject with IAI at a frequency per his/her discretion.

5.5 Dose Modification and Stopping Rules

5.5.1 Dose Modification

Dose modification for an individual subject is not allowed.

5.5.2 Study Drug Stopping Rules

Subjects who discontinue from study drug will be exited from the study and must perform an Early Termination Visit approximately one month following last dose of study drug.

5.5.2.1 Reasons for Permanent Discontinuation of Study Drug:

The subject may be withdrawn from the study for any reasons: if it is in the best interest of the subject, illness, adverse events, or worsening condition. The PI may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

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

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

- Sensory rhegmatogenous retinal detachment or Stage 3 or 4 macular hole
- Investigator determination that it is not in the best interest of the subject to continue participation
- Pregnancy

- Need for anti-VEGF therapy other than IAI in either eye for a condition requiring treatment other than AMD.
- 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.

5.5.2.2 Reasons for Temporary Discontinuation of Study Drug

Temporary discontinuation is not allowed in the study.

5.6 Method of Treatment Assignment

Subjects will be randomized in a 1:1 ratio to treatment and observations groups by simple random assignment.

5.6.1 Masking

Subjects will be masked to the identity of treatment (IAI or observation). Sham injections will be performed to preserve the mask. When performing a sham injection, the ophthalmologist will ensure that injection preparation is identical to an IAI injection besides the actual injection.

5.6.2 Emergency Unmasking

Emergency unmasking of treatment assignment for a subject may be necessary due to a medical emergency, a serious adverse event SAE that is unexpected and for which a causal relationship to study drug cannot be ruled out, or any other significant medical event (e.g. pregnancy).

If emergency unmasking is required for a medical emergency:

- Only an investigator will make the decision to unmask the treatment assignment.
- Only the subject with the medical emergency will be unmasked.
- The investigator or coordinator will notify Regeneron and/or designee that the subject has been unmasked.

5.7 Treatment Logistics and Accountability

5.7.1 Packaging, Labeling, and Storage

2.0 mg intravitreal aflibercept injection is formulated as a sterile liquid to a final concentration of 40 mg/mL intravitreal aflibercept injection in 5% sucrose, 10 mM sodium phosphate pH 6.3, 0.03% polysorbate 20, and 40 mM NaCl. Intravitreal aflibercept injection 2.0 mg study drug will be supplied by Regeneron Pharmaceuticals Inc. in sealed, sterile 3 mL vials with a "withdrawable" volume of approximately 0.5 mL. Vials must be used only once (defined as entered with a needle). The volume of injection will be 0.05 mL for the 2 mg dose. For study drug in vials, the study drug will be withdrawn using aseptic technique.

Study drug will be shipped to the site via overnight shipping using cold packs to maintain a temperature of 2° to 8° C. The investigator, or an approved representative (e.g. pharmacist), will ensure that all study drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. The shipping box is to be opened and stored immediately at the site in a refrigerator intended for investigational products at a temperature of 2° to 8°C.

When vials are removed from the refrigerator, the solution should be visually inspected and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Exposure of the material to temperatures outside these limits, except for warming prior to administration, is not recommended and may result in loss of activity. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained; and must include a record of the dates, when the refrigerator was checked, the initials of person checking, and the temperature.

5.7.2 Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2 to 8ºC to the investigator or designee at regular intervals or as needed during the study. During site close-out, and following drug reconciliation and documentation, all unopened vials of study drug will be destroyed.

5.7.3 Treatment Accountability

All drug accountability records will be kept current.

The investigator will account for all opened and unopened vials of study drug. These records will contain the dates, quantity, and study medication

- dispensed to each subject,
- returned from each subject (if applicable), and
- disposed of at the site.

All accountability records will be made available for inspection by regulatory agency inspectors.

5.7.4 Treatment Compliance

All drug compliance records will be kept current and will be made available for inspection by regulatory agency inspectors.

5.8 Concomitant Medications and Procedures

Subjects may take oral AREDS formula vitamins during the study.

IAI will be provided, as needed, for the subject's fellow eye and may be administered per investigator's discretion. If a subject is currently receiving therapy in his fellow eye other than IAI, treatment will be switched to IAI. IAI is the only treatment allowed by the study for the treatment of neovascular AMD. Subject may not have received any treatment for exudative AMD other than IAI in his fellow eye within 28 days prior to Day 0.

5.8.1 Permitted Medications and Procedures

Upon confirmation of conversion of study eye to neovascular AMD, the investigator will treat subject with IAI at a frequency per his/her discretion.

5.8.2 Prohibited Medications and Procedures

No other treatment for choroidal neovascularization should be given to the study eye, including, but not limited to, laser photocoagulation, photodynamic therapy, pegaptanib therapy, transpupillary thermotherapy, external beam radiation therapy, submacular surgery, or other surgical intervention for AMD.

No other experimental or investigational treatments are permitted during this study; this includes ocular experimental and investigational treatments in the study eye.

Elective vitrectomy surgery is not allowed in the study eye during study participation. Onset of glaucoma during study participation should be treated as clinically indicated. Cataract surgery in the study eye may be performed if clinically indicated and should occur > 30 days after the previous study injection.

Treatment of CNV in the non-study eye during the follow-up period should follow the best medical judgment of the treating ophthalmologist for the subject.

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

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

6.1 Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1.

Table 1 Schedule of Events

Day	Screening	Baseline/ Day 0	Month 3[F]	Month 6	Month 9[F]	Month 12	Month 15[F]	Month 18	Month 21[F]	Month 24/ Early Term	Suspected Conversion Visit (SCV)[A]
Informed Consent	X										
Inclusion/Exclusion	X										
Medical/Ophthalmic History	X										
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
ETDRS Refraction & Visual Acuity	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Exam: SLE & DFE	X	X	X	X	X	X	X	X	X	X	X
SD-OCT[B]	X	X	X	X	X	X	X	X	X	X	X
OCT Angiography[B]	X	X	X	X[F]	X	X[F]	X	X[F]	X	X[F]	X
Fundus Photography[B]	X	X				X[F]				X[F]	X[A]
Fluorescein Angiography[B]	X	X	X	X[F]	X	X[F]	X	X[F]	X	X	X[A]
Administer Study Drug or Sham Injection		X	X	X[F]	X	X[F]	X	X[F]	X		
Adverse Events		X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[C]	X										
Blood Sample[D]		X									
At-home Monitoring[E]											

A – See Section 6.2.5 for discussion of SCV. FA and FP performed per investigator discretion. If investigator believes conversion has occurred, FA must be performed and submitted to reading center along with SD-OCT for confirmation of conversion prior to treatment.
B – Study eye only.
C – Women of child-bearing potential (WOCBP) only.
D – For subjects participating in genomics sub-study only.
E – For subjects participating in home monitoring sub-study only. See Appendix A for at-home monitoring procedures.
F – Visit or assessment is not required if confirmation of conversion to exudative AMD in study eye precedes the visit.

6.2 Study Visit Descriptions

6.2.1 Screening/Day –14 to Day -1 (window)

After the subject has provided informed consent, the following information will be collected:

- Inclusion/exclusion
- Demographics
- Medical and ophthalmic history
- Concomitant medications
- Date of initial fellow eye diagnosis of exudative AMD

The following procedures and assessments will be conducted:

- Vital signs including sitting blood pressure, and pulse
- Urine pregnancy test for WOCBP only
- ETDRS refraction and visual acuity (VA) testing
- Ophthalmic exam including slit lamp exam (SLE) and dilated fundus exam (DFE)
- Spectral-domain optical coherence tomography (SDOCT) using Avanti device
- OCT angiography using Avanti AngioVue™
- Fundus photography (FP)
- Fluorescein angiography (FA)

6.2.2 Treatment Period

6.2.2.1 Baseline/Day 0

The Baseline/Day0 visit may occur on the same day as the Screening visit. If this is the case, the assessments performed at Screening do not need to be repeated.

The following information will be collected:

- Concomitant medications

The following procedures and assessments will be conducted:

- Vital signs including sitting blood pressure, and pulse
- For subjects participating in home monitoring sub-study, train subject on proper usage of the Paxos Checkup™ app (see Appendix A for specific procedures)
- ETDRS refraction and VA testing
- Ophthalmic exam including SLE and DFE
- SDOCT using Avanti device
- OCT angiography using Avanti AngioVue™
- FP
- FA
- Blood draw for genomic testing
- Administer IAI or sham injection
- Assess adverse events

6.2.2.2 Month 3, 6, 9, 12, 15, 18, 21 (window: ± 7 days for each visit)

The following information will be collected:

- Concomitant medications
- Assess adverse events

The following procedures and assessments will be conducted:

- Vital signs including sitting blood pressure, and pulse
- ETDRS refraction and VA testing
- Ophthalmic exam including SLE and DFE
- SDOCT using Avanti device
- OCT angiography using Avanti AngioVue™
- FA

- FP (Month 12 only)
- Administer IAI or sham injection, unless conversion to neovascular AMD is confirmed at current visit. If this is the case, initiate IAI therapy per investigator's discretion.

6.2.3 End of Study Visit/ Month 24 (window: ± 7 days)/ Early Termination

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Vital signs including sitting blood pressure, and pulse
- ETDRS refraction and VA testing
- Ophthalmic exam including SLE and DFE
- SDOCT using Avanti device
- OCT angiography using Avanti AngioVue™
- FA
- FP
- For subjects participating in home monitoring sub-study, ensure subject returns any loaned device, if applicable.

6.2.4 Early Termination Visit

Subjects who are withdrawn from the study should be instructed to return to the clinic for end of study assessments, as described in section 6.2.3.

6.2.5 Suspected Conversion Visits (SCV)

Given the nature of the subject population, unscheduled visits due to suspected conversion to neovascular AMD are likely. These visits may be prompted by vision changes or other complaints in subject's study eye or an alert from the home monitoring app (for participating subjects). In the

event of an alert from the home monitoring app, the study investigator or designee should promptly review the home testing data in the app, speak to the subject, if appropriate, and decide whether to bring the subject in for an SCV.

The following information will be collected:

- Concomitant medications
- Assess adverse events

The following procedures and assessments will be conducted:

- Vital signs including sitting blood pressure, and pulse
- ETDRS refraction and VA testing
- Ophthalmic exam including SLE and DFE
- SDOCT using Avanti device
- OCT angiography using Avanti AngioVue™

The following procedures may be performed per investigator's discretion:

- FA
- FP

If investigator believes that conversion to neovascular AMD has occurred, then FA must be performed and sent to the reading center along with the SDOCT for confirmation prior to treatment.

If confirmed by reading center, initiate IAI therapy per investigator's discretion.

6.2.6 Other Interim Visits

If subject is seen at an interim visit for a reason that is unrelated to his/her study eye, **subject's study eye should not be examined or evaluated**.

6.2.7 Required Visits Post-Conversion

If there is a confirmed conversion to neovascular AMD in the subject's study eye during the study, the subject will stay in the study and will be treated with IAI. The frequency of office visits, testing procedures, and treatment with IAI is at the investigator's discretion, according to standard care.

The following study visits will **not** be required if conversion precedes the visit: Month 3, Month 9, Month 15, and Month 21.

Following conversion, required study visits will include: Month 6, Month 12, Month 18, and Month 24, only. Assessments at these required visits are the same as listed for the respective visits above, except that OCT-A, FP, and administration of IAI or sham will not be required. OCT-A, FP, and administration of IAI may be performed per investigator's discretion. If OCT-A, and FP are performed at these visits following conversion, they should **not** be submitted to the reading center.

FA will also **not** be required at the Month 6, Month 12, or Month 18 visits, if the visits follows a confirmed conversion. However, FA is required at the Month 24 visit and should be submitted to the reading center.

Furthermore, in the event of conversion to neovascular AMD, required study visits occurring after conversion (e.g. Months 6, 12, 18, 24) may be performed +/- 30 days from the target date rather than +/- 7 days from the target date.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1 Definitions

7.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered a study drug, which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (i.e. any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

7.1.2 Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (e.g. a car accident in which a subject is a passenger).
- Is **life threatening** – in the view of the investigator, the subject is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or prolongation of existing hospitalization. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent 1 of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse). Any malignancy (other than basal cell skin cancers) would be considered a medically important event.

7.2 Recording and Reporting Adverse Events

All AEs and SAEs will be recorded on the CRF and in the subject's source documents. Ophthalmic exam or vital signs abnormalities will be recorded as AEs only if they are deemed clinically significant by the investigator.

All SAEs, regardless of assessment of causal relationship to study drug will be reported to Regeneron Pharmaceuticals, Inc.

The investigator will promptly report to the IRB all unanticipated problems involving risks to subjects. This includes death from any cause and all SAEs related to the use of the study drug. All SAEs will be reported to the IRB, regardless of assessed causality.

7.2.1 Deaths

Any AE that results in death is considered an SAE. Deaths that occur from the time the subject signs the informed consent form ("ICF") until 90 days after dosing will be reported to the appropriate IRB and to Regeneron Pharmacovigilance and Risk Management (or designee) within 24 hours of learning of the death.

Any available autopsy reports and relevant medical reports will be sent to Regeneron Pharmaceuticals, Inc. as soon as possible.

To report an SAE, Regeneron will be contacted at the following:

Medical.safety@regeneron.com
Fax 914-345-7476
SAE hotline: 914-593-1504

7.2.2 Pregnancy and Other Events that Require Accelerated Reporting

The following events will be reported to Regeneron Pharmaceuticals, Inc. within 24 hours of learning of the event:

Overdose: Accidental or intentional overdose of the study drug or concomitant medication, whether or not it is considered an AE.

Pregnancy: Although it is not considered an AE, the investigator will report to Regeneron Pharmaceuticals, Inc., any pregnancy occurring in a female subject or female partner of a male

subject, during the study or within 90 days following the last dose of study drug. The investigator will follow the pregnancy until delivery, or longer. If the pregnancy continues to term (delivery), the health of the infant will also be reported to Regeneron Pharmaceuticals, Inc.

To report an SAE, Regeneron will be contacted at the following:

Medical.safety@regeneron.com
Fax 914-345-7476
SAE hotline: 914-593-1504

7.2.3 Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a subject's withdrawal from the study will be reported to Regeneron Pharmaceuticals Inc. within 30 days. All SAEs leading to a subject's withdrawal from the study will be reported. To report an SAE, Regeneron will be contacted at the following:

Medical.safety@regeneron.com
Fax 914-345-7476
SAE hotline: 914-593-1504

7.2.4 Abnormal Vital Signs Results

The criteria for determining whether an abnormal objective test finding will be reported as an AE are as follows:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

7.2.5 Follow-up

Adverse event information will be collected until the end of study visit, or the early termination visit, if the subject withdraws consent.

The investigator must make every effort to obtain follow-up information on the outcome of any SAE until the event is considered chronic and/or stable.

7.3 Evaluation of Severity and Causality

7.3.1 Evaluation of Severity

The severity of an AE will be graded by the investigator using a 3–point scale (mild, moderate, or severe) and reported in detail as indicated on the CRF and/or SAE form, as appropriate.

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

7.3.2 Evaluation of Causality

The relationship to treatment will be determined by the investigator and reported on the CRF and/or SAE form, as appropriate. The following terms will be used:

Not Related: likely or clearly due to causes other than the study drug.

Related: possibly, probably, or definitely related to the study drug.

8. STUDY VARIABLES

8.1 Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (e.g. age, race, etc.), disease characteristics including medical history, and medication history for each subject.

8.2 Primary and Secondary Endpoints

The primary endpoint in the study is the proportion of subjects converting to neovascular AMD at 24 months, characterized by the development of choroidal neovascularization (CNV). The development of CNV will be assessed by:

- CNV leakage on FA, and
- Evidence of any fluid on SD-OCT.

Conversion will be confirmed by the reading center. The Kaplan-Meier method will be used to estimate time to conversion using the conversion criteria, and the log-rank test will be used to compare the time course among treatment groups.

The secondary endpoints are:

- Mean change in visual acuity at 12 months and 24 months compared to baseline;
- Percentage of subjects losing < 15 ETDRS letters at 12 months and 24 months as compared to baseline;
- Incidence and severity of potential ocular side effects including endophthalmitis, retinal detachment, cataract, and intraocular inflammation
- Incidence and severity of systemic side effects; and
- Development/progression of geographic atrophy.

In subjects who choose to participate in the genomics sub-study, blood samples will be taken for exploratory DNA analysis.

In subjects who convert to neovascular AMD, additional exploratory analyses include:

- Mean change in visual acuity at conversion;
- Mean change in visual acuity at 24 months;
- Mean number of IAI injections through Month 24
- Mean size of choroidal neovascular membrane at 24 months per FA
- Detection of conversion to neovascular AMD by OCT angiography
- Correlation of CNV detection by OCT angiography relative to FA
- Timing of CNV detection by OCT angiography relative to FA.

In subjects who choose to participate in the home monitoring sub-study, exploratory analyses include the correlation between an alert generated by Paxos Checkup™ application ("app") and a confirmed conversion at subject's next office visit.

9. STATISTICAL PLAN

9.1 Statistical Hypothesis

The percentage of subjects who convert to neovascular AMD in the study eye through months 12 and 24 will be examined by treatment group.

Chi-square tests for contingency tables will be used to compare conversion rates between subjects whose study eyes were randomized to control (sham) versus IAI.

The Kaplan-Meier method will be used to estimate time to conversion using the conversion criterion, and the log-rank test will be used to compare the time course among treatment groups.

For converters, time to conversion will be calculated as number of days between first treatment date and first conversion date defined as SD-OCT and/or FA examination date, onset date for adverse event, procedure date for concurrent ocular procedure, and start date for concomitant medication.

For non-converters, follow-up time will be calculated as days from first treatment date to last study date. Statistical significance will be defined as $P < .05$.

The primary statistical analyses will be performed on an intent-to-treat basis.

9.2 Determination of Sample Size

Sample sizes were calculated by setting the power at .80 and the alpha level at .05 for detecting a 70% reduction in conversion to neovascular AMD yielding N = 102 subjects (51 treatment and 51 control).

Prior studies have shown that, of those who had neovascular AMD in one eye, conversion rates from non-neovascular to neovascular AMD in high-risk fellow eyes was 10-60% over 1-2 years. We assume a 35% conversion rate over 2 years.

An assumed 8% loss due to death and dropouts per year was used for all calculations.

9.3 Analysis Sets

9.3.1 Efficacy Analysis Sets

The full analysis set ("FAS") includes all randomized subjects who received any study drug; it is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

9.3.2 Safety Analysis Set

The safety analysis set ("SAF") includes all randomized subjects who received any study drug; it is based on the treatment received (as treated). Treatment compliance/ administration and all clinical safety variables will be analyzed using the SAF.

9.4 Subject Disposition

The following will be provided:

- The total number of screened subjects who met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized subjects who received a randomization number
- The total number of subjects in each analysis set (e.g.FAS, SAF, etc.)
- The total number of subjects who discontinued the study, and the reasons for discontinuation

9.5 Statistical Methods

9.5.1 Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group. Continuous variables will be summarized with mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

9.5.2 Efficacy Analyses

Efficacy endpoints from all enrolled subjects will be analyzed by treatment group.

9.5.3 Safety Analysis

Adverse events from all enrolled subjects will be utilized to summarize safety data by treatment group.

9.5.4 Interim Analysis

After all subjects have completed the Month 12 visit, the following will be analyzed:

- Proportion of subjects converting to neovascular AMD at 12 months, characterized by the development of choroidal neovascularization (CNV). The development of CNV will be assessed by:
    - CNV leakage on FA, and
    - Evidence of any fluid on SD-OCT.

  Conversion will be confirmed by the reading center ("confirmed conversion").
- Mean change in visual acuity at 12 months compared to baseline
- Percentage of subjects losing < 15 ETDRS letters at 12 months as compared to baseline
- Incidence and severity of potential ocular side effects including endophthalmitis, retinal detachment, cataract, and intraocular inflammation
- Incidence and severity of systemic side effects

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at the study site.

The CRF data for this study will be collected on paper-based forms and transmitted to the contract research organization (CRO) for data entry into the study database, a Microsoft Access database.

10.1 Electronic Systems

Electronic systems used to process and/or collect data in this study will include the following:

- Study sites' electronic medical records systems.
- Microsoft Access-based database designed and maintained by the study CRO.

11. STUDY MONITORING

11.1 Monitoring of Study Sites

The study monitor and/or designee (e.g. CRO monitor) will visit each site prior to enrollment of the first subject, and periodically during the study. In accordance with International Conference on Harmonisation ("ICH") guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, subject ICFs, documentation of subject recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log will be provided to the study monitor upon request.

11.2 Source Document Requirements

Investigator will prepare and maintain adequate and accurate subject records (source documents).

The investigator will keep all source documents on file with the CRF. Case report forms and source documents will be available at all times for inspection by authorized representatives of the regulatory authorities.

11.3 Case Report Form Requirements

A CRF for each subject enrolled in the study will be completed and signed by the study investigator or authorized designee. The CRF will be typed or filled out using indelible ink. The writing will be legible. Errors will be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or authorized designee. The investigator will ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs. Case report forms will be available at all times for inspection by authorized representatives of the regulatory authorities.

12. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the regulatory authorities. Should this occur, the investigator will be responsible for:

- Informing Regeneron of a planned inspection by the authorities as soon as notification is received
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the Regeneron immediately
- Taking all appropriate measures requested by the regulatory authorities to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection.

In all instances, the confidentiality of the data will be respected.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice Statement

It is the responsibility of the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

13.2 Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP.

Regeneron will have the right to review and comment on the informed consent form.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each subject prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the subject in language that he/she can understand. The ICF will be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

Subjects who can write but cannot read will have the ICF read to them before signing and dating the ICF.

Subjects who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF will be retained by the investigator as part of the subject's study record, and a copy of the signed ICF will be given to the subject.

If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated appropriately. All study subjects will be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF will be maintained in the subject’s study record and a copy will be given to the subject.

13.3 Subject Confidentiality and Data Protection

The investigator will take all appropriate measures to ensure that the anonymity of each study subject will be maintained.

The subject's and investigator's personal data will be treated in compliance with all applicable laws and regulations.

13.4 Institutional Review Board

An appropriately constituted IRB/IEC, as described in ICH Guidelines for GCP, will review and approve:

- The protocol, ICF, and any other materials to be provided to the subjects (e.g. advertising) before any subject may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the IRB will be informed as soon as possible

Ongoing studies will be reviewed by the IRB/EC on an annual basis or at intervals appropriate to the degree of risk.

In addition, the IRB will be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study.

A copy of the IRB approval letter will be sent to Regeneron prior to shipment of drug supplies to the investigator. The approval letter will include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB review and approval of all study documents (including approval of ongoing studies) will be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The investigator will not implement a change in the design or operation of the protocol or ICF without an IRB-approved amendment.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1 Premature Termination of the Study

The investigator will notify Regeneron of a desire to close-out a site in writing, providing approximately 30 days' notice. The final decision will be made through mutual agreement with Regeneron. Both parties will arrange the close-out procedures after review and consultation.

In all cases, the appropriate IRB and Health Authorities will be informed according to applicable regulatory requirements, and adequate consideration will be given to the protection of the subjects' interests.

16. STUDY DOCUMENTATION

16.1 Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs will be signed by the investigator. This certification form accompanies each set of CRFs.

16.2 Retention of Records

The investigator will retain all essential study documents, including ICFs, source documents, CRFs, and drug accountability records for at least 10 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. Records will be destroyed in a manner that ensures confidentiality.

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

1. Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 2004;122:477–485.

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3. Bressler NM, Bressler SB, Fine SL. Age-related macular degeneration. Surv Ophthalmol 1988;32(6):375–413.

4. Age-related Eye Disease Study Research Group. Risk factors for the incidence of advanced age-related macular degeneration in the age-related eye disease study (AREDS)- AREDS Report No. 19. Ophthalmology 2005; 112(4):533-539.

5. Barbazetto IA, Saroj N, Shapiro H, Wong P, Ho AC, Freund KB. Incidence of new choroidal neovascularization in fellow eyes of patients treated in the MARINA and ANCHOR trials. Am J Ophthalmol. 2010 Jun;149(6):939-946.

6. Lujan BJ, Zhengrong L, Hopkins JJ. Comparison of spectral domain (SD-OCT) and fluorescein angiography (FA) conversion rates in fellow eyes of harbor patients. AAO 2012 Joint Meeting Poster # PO241. Chicago, IL, November 10-13th.

7. Age-related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119: 1416–36.

APPENDIX A - Paxos Checkup™ Application Procedures

21. APPENDIX A PAXOS CHECKUP™ APPLICATION PROCEDURES

21.1 For the Practice Sites

Practice sites will be trained by DigiSight Technologies, Inc. prior to subject enrollment so that staff are certified to:

- Register monitoring subjects on the Paxos Checkup™ app
- Configure subject test sequence (Acuity and Amsler) and frequency (bi-weekly)
- Prepare subjects for home monitoring ("onboarding")
- Review monitoring data for testing compliance and vision alerts
- Respond per study protocol to vision alerts

Physicians and staff will also be registered on the DigiSight system (required to review patient monitoring information), and practices configured (so that data sharing between physicians and staff may occur) prior to study start.

21.2 For the Subject

Once subjects have been enrolled in the monitoring sub-study, they will be registered and "onboarded" by site staff following procedures documented in:

How to Register New Patients

How to Prepare New Patients for Home Vision Monitoring

The onboarding process will be accomplished during the subject's baseline visit, when subject is not dilated.

Following the baseline visit, the subject will monitor at home, running "My Test Sequence" to do his/her Acuity and Amsler tests at least twice per week. Optimally, subject will test around the same time of day and in the same conditions, but this is not required.

Subject will be reminded if he/she fails to test at least twice per week, and must respond to any reminders, or instructions from the app to re-test, promptly.

Failure to maintain testing compliance will be grounds for removal from the sub-study, at the site physician's determination.

Because monitoring data must flow to the practices in real time, subjects using devices without cell service which require network connectivity (for example, iPods and certain iPads) must ensure that they are connected (for example, via WiFi) when testing. If the subject cannot maintain connectivity reliably during the study, this may be grounds for removal from the sub-study, at the site physician's determination.

If the subject receives a vision alert on his/her testing device, he/she should follow the instructions from the application and call his/her physician's office to discuss promptly. If he/she feels the alert was generated by a testing error, he/she should make this clear to the office at the time of discussion.

Please note that the subject should NEVER WAIT TO CONTACT HIS/HER PHYSICIAN IF HE/SHE EXPERIENCES A CHANGE IN HIS/HER VISION because of something learned in connection with the app, nor should he/she assume that a vision alert received in the app necessarily corresponds to a significant event in the progression of his/her disease, but must follow study protocol and contact the office when a vision alert is received.

If the subject requires technical support on any issue having to do with the Paxos Checkup™ application or www.digisight.net website for the duration of the sub-study, he/she may contact info@digisight.net or call (650) 223-5560 to receive timely technical support.

If the subject requires help with any non-technical (medical) issues for the duration of the sub-study, he/she should contact his/her physician or physician's office.

If a loaner device is used for the duration of the study, it will be returned to DigiSight Technologies, Inc. at the subject's exit or withdrawal.