Clinical Study Protocol

Intravitreal Aflibercept Injection for Radiation Retinopathy Trial (ARRT)

Compound:	Intravitreal aflibercept injection
Study Name:	**Intravitreal Aflibercept Injection for Radiation Retinopathy Trial (ARRT)**
Clinical Phase:	II
Date of Issue:	01 Mar 2018
Primary Investigator:	Amy Schefler, MD

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE	Intravitreal aflibercept injection (IAI) for Radiation Retinopathy Trial (ARRT)
SITE LOCATION(S) **Principal Investigator**	6560 Fannin, Ste. 750 Houston, TX 77030 23501 Cinco Ranch Blvd., Ste. G205 Katy, TX 77494 17350 St. Luke's Way, Ste. 120, The Woodlands, TX 77384 5030 Cascade Rd, SE, Grand Rapids, MI 49546 Amy C. Schefler, MD
OBJECTIVE(S)	Primary Objective ARRT trial will assess the safety of intravitreal injections 2 mg Aflibercept (IAI) for radiation retinopathy including maculopathy and optic neuropathy at week 52. <u>Secondary Objectives:</u> • Mean number of IAI received from baseline through week 52 • Resolution of macular edema (mean change in CRT; % patients whose achieve a dry macula) at week 52 • Stabilization and improvement in BCVA at week 52 • Percentage of patients avoiding the development of increased neovascularization, vitreous hemorrhage, and need for vitrectomy at week 52 • Percentage of patients with resolution of retinal hemorrhages, retinal exudates, optic disc edema, capillary nonperfusion at week 52
STUDY DESIGN	Open-label
STUDY DURATION	52 weeks
ESTIMATED STUDY COMPLETION DATE	January 2019
POPULATION	
Sample Size:	Expected total number of population is 30
Target Population:	Men and women 18 years and older with radiation retinopathy
TREATMENT(S)	
Study Drug	2 mg IAI
Dose/Route/Schedule:	Study eyes will be assigned randomly (1:1 ratio) to one of the following treatment arms: <u>Group 1</u>: Receive a loading dose of 3 consecutive IAI, followed by a treat and extend protocol <u>Group 2</u>: Treat and extend protocol
ENDPOINT(S)	
Primary:	The ARRT trial will assess the safety of intravitreal injections of 2 mg Aflibercept (IAI) for radiation retinopathy at 52 weeks.

Secondary:	• Mean number of IAI received from baseline through week 52 • Resolution of macular edema (mean change in CRT; % patients whose achieve a dry macula) at week 52 • Stabilization and improvement in BCVA at week 52 • Percentage of patients avoiding the development of increased neovascularization, vitreous hemorrhage, and need for vitrectomy at week 52. • Percentage of patients with resolution of retinal hemorrhages, optic disc edema, capillary nonperfusion at week 52
PROCEDURES AND ASSESSMENTS	Visual function of the study eye and the fellow eye will be assessed using the 4-meter ETDRS protocol. The anatomical state of the retinal vasculature of the study eye and the fellow eye will be evaluated by funduscopic examination, FA, and FP. Anatomic characteristics will be evaluated using SD-OCT and OCT-A (utilizing Optovue Angio-Vue system if available). Overall safety will be assessed by monitoring/evaluating adverse events (AE's) and vital signs. Ocular safety will be assessed by ophthalmic examinations (intraocular pressure [IOP], slit lamp examination, and indirect ophthalmoscopy)

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1. INTRODUCTION AND RATIONALE

1.1 Introduction

Radiation retinopathy is a common and devastating visual side effect of brachytherapy treatment for uveal melanoma. Treatment methods for visual stabilization or improvement in these patients are sorely needed. Although local tumor control rates in the Collaborative Ocular Melanoma Study (COMS) and other reports are excellent for small to medium-sized choroidal melanoma,[1] long-term visual acuity outcomes have been poor for many patients. In the COMS report examining visual outcomes post-treatment at 3 years noted, 43% of patients had a visual acuity of 20/200 or worse and 49% had a loss of six or more lines from the pre-treatment level.[2] Furthermore, in the COMS, as soon as a poor visual outcome was observed, improvement in vision to a level that no longer met the definition of poor vision was rare. The most common reason for irreversible vision loss is radiation retinopathy. In Kaplan-Meier analysis, rates of non-proliferative and proliferative disease at 5 years after plaque therapy are: 42% and 8%, respectively.[3] Since most epidemiologic studies suggest that there are 1,500-2,000 new uveal melanomas diagnosed in the U.S. each year, the data suggests that there are likely up to 10,000 patients alive and living with active radiation retinopathy who have been treated with brachytherapy during the past 10 years in the U.S. alone.

There have only been several small published studies thus far on the use of anti-VEGF injections for radiation retinopathy, most of which have 5 or fewer patients and very few of which are prospective.[5-12] There have been no large-scale studies published on the use of IAI for radiation retinopathy. The purpose of this study is to evaluate the safety of IAI for radiation retinopathy as well as to explore two different dosing regimens for use in this condition.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to assess the safety of 2 mg intravitreal Aflibercept injections (IAI) for the treatment of radiation retinopathy including maculopathy and optic neuropathy.

2.2 Secondary Objective(s)

The secondary objectives of the study are:

- Resolution of macular edema (mean change in CRT; % patients who achieve a dry macula) at week 52
- Stabilization and improvement in BCVA at week 52
- Dosing frequency of IAI as measured by number of injections
- Percentage of patients avoiding the development of increased neovascularization, vitreous hemorrhage, and need for vitrectomy at week 52.
- Percentage of patients with resolution of retinal hemorrhages, retinal exudates, optic disc edema, capillary non-perfusion

3. STUDY DESIGN

3.1 Study Description and Duration

The ARRT trial will assess the safety and efficacy of 2mg IAI for the treatment of radiation retinopathy, including maculopathy and optic neuropathy.

3.2 Planned Interim Analysis

No interim analysis planned

3.3 Study Committees

3.3.1 Independent Data Monitoring Committee

No independent data monitoring committee

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1 Number of Patients Planned

A total of approximately 30 patients with radiation retinopathy will be enrolled in the US.

4.2 Study Population

The study population will be men or women ≥ 18 years or older with radiation retinopathy associated with previous treatment from radiation plaque, proton beam, or orbital radiation therapy.

4.2.1 Inclusion Criteria

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

1. Age ≥ 18 years of age
2. Clinically identifiable radiation retinopathy with evidence of fluid on SD-OCT causing vision loss in the study eye
3. Undergone either ocular or orbital radiation for any primary ocular or orbital cancer within clinical evidence of having radiation retinopathy
4. Willing and able to comply with clinic visits and study-related procedures
5. Provide signed informed consent

4.2.2 Exclusion Criteria

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

1. Metastatic cancer or any active primary cancer, at time of enrollment
2. Prior treatment with anti-VEGF in the study within 60 days of screen in the study eye
3. Prior intravitreal or subconjunctival treatment with cortical steroids within 90 days of screen in the study eye
4. Macular ischemia (defined as greater than 5 disc areas), as assessed by the investigator
5. Media opacity obscuring a view of the fundus or any other reason for vision loss other than radiation retinopathy.
6. Evidence of infectious ocular infection, in the study eye, at time of screening
7. Pregnant or breast-feeding women
8. Sexually active men* or women of childbearing potential** who are unwilling to practice adequate contraception from start of the first treatment, during the study, and for at least 3 months after the last dose. Adequate contraceptive measures can

include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device; 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 childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

4.3 Premature Withdrawal from the Study

A patient 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 patient from the study in the event of an intercurrent 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 patients will be avoided. Should a patient (or a patient'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 Patients

Patients prematurely withdrawn from the study can be replaced, if needed, to ensure an adequate number of evaluable patients.

5. STUDY TREATMENTS

The investigational product is intravitreal aflibercept injection, which will be supplied by Regeneron Pharmaceuticals, Inc. in sterile vials for intravitreal (IVT) injection. The study duration will be 52 weeks. Vials of drug must be used (defined as entered with needle) only once. All drug supplies are to be kept under recommended storage

conditions. The injection volume will be 50µL (0.05 mL) and will be administered to the patients by IVT injection.

Approximately 30 eyes will be randomized (1:1 ratio) into either Group 1 or Group 2. Slit lamp exam and Indirect ophthalmoscopy will be performed at every study visit, where retinopathy level will be assessed, See Appendix II for grading scale. SD-OCT will be performed at each visit. Fluorescein angiogram will be performed at screen, week 26 and week 52. All other imaging studies will be standard of care at the discretion of the investigator.

This trial will compare the results of 2 groups, with different treatment intervals, to assess the safety of IAI for the treatment of radiation retinopathy. Patients in each group will be followed for a total of 52 weeks.

Group 1: 15 Patients will receive a loading dose of 3 IAI. They will receive 2 mg IAI at screening/baseline, week 4, week 8.. A follow-up visit will occur at week 12. If the extension criteria are met, the patient will be treated and then extended by 2 weeks. The patient will continue to be followed per the treat and extend protocol described below.

Group 2: Patients will not receive a loading dose. They will receive 2 mg IAI at screening/baseline followed by a visit at week 4. At week 4, if the extension criteria are met, the patient will be treated and then extended by 2 weeks. The patient will continue to be followed per the treat and extend protocol described below.

Treat & Extend Protocol

Patients can be extended as long as they meet the following criteria –

- Absence of retinal fluid (resolution of intraretinal and subretinal fluid on SD-OCT; Small intraretinal cysts that do not distort foveal contour on SD-OCT are acceptable and can be considered "dry".)
  AND
- Less than 5 ETDRS letter loss from previous visit due to new or persistent retinal

edema.

IAI will be rendered at every visit (treatment at the week 26 mandatory visit will be administered based on the treat and extend status), no earlier than 4 days before the target date and no later than 4 days after the target date. Each extension will be 2 weeks in duration beyond the initial 4-week interval. If the extension criteria are not met on a follow-up visit, the treatment interval will be reduced by 2 weeks. Follow up interval will continue to be reduced by 2 weeks until the extension criteria are met or a 4-week interval is reached.

All patients will have a mandatory study visit at Week 52 (final study visit). No study treatment will be administered after week 50 or at a study termination visit. If a patient receives treatment after week 48, they will return 4 weeks after the last clinic visit for the final study visit (instead of at week 52).

5.1 Treatment Logistics and Accountability

5.1.1 Packaging, Labeling, and Storage

Study drug will be refrigerated at the site at a temperature of 2 to 8º C; refrigerator temperature will be logged daily. At no time, will product be left unattended or outside the control of an individual knowledgeable with regard to product temperature requirements. Failure to maintain 2° to 8°C temperature control will likely result in unusable product. Moreover, no one will administer product that has not been maintained according to temperature requirements.

5.1.2 Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2 to 8º C 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 opened and unopened vials of study drug will be destroyed -or- returned to Regeneron Pharmaceuticals, Inc. or designee.

5.1.3 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 patient,
- disposed of at the site or returned to Regeneron Pharmaceuticals, Inc. or designee.

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

5.1.4 Treatment Compliance

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

5.2 Concomitant Medications

Any medication administered from the first dose of IAI to the final study visit will be considered concomitant medication.

5.2.1 Prohibited Medications

Study Eye

Patients may not receive any standard or investigational agents in their study eye other than IAI.

Fellow Eye

Patients may receive any standard of care therapies necessary for treatment in the fellow eye other than anti-VEGF drugs.

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 2.

Table 1 Group 1 and 2 Schedule of Events

	Screening/ Baseline	**Week 4 - 25**[3] (+/- 4 days)		**Week 26** (+/- 4 days)	**Week 27-48**[3] (+/- 4 days)	**Week 52/ Early Term** (+/- 4 days)
Informed Consent	X					
Demographics	X					
Medical/Ophthalmic History	X					
Vitals	X					
Pregnancy Test[1]	X					
Inclusion/ Exclusion	X					
Concomitant Medications	X	X		X	X	X
Adverse Events	X	X		X	X	X
BCVA (ETDRS)	X	X		X	X	X
Intraocular Pressure	X	X		X	X	X
SD-OCT (OU)	X	X		X	X	X
OCT-A (OU)[2]	X			X		X
Optos Fundus Photography	X			X		X
Optos Fluorescein Angiography	X			X		X
Indirect Ophthalmoscopy/ Slit Lamp	X	X		X	X	X
Study Drug Treatment	X	X		X[4]	X	

1) Urine pregnancy test for women of child bearing potential
2) Performed at sites with capability
3) Treatment Interval depends on pre-specified criteria
4) Treatment at week 26 is not mandatory and will be administered based on patients treat and extend status

						)

6.2 Study Visit Descriptions

6.2.1 Screening/Baseline

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

- Inclusion/exclusion

- Demographics
- Medical history and concurrent illnesses
- Concomitant medications

The following procedures and assessments will be conducted:

- Vital Signs
- Urine pregnancy test (if applicable)
- IOP (pre-dose bilateral)
- SD-OCT (OU)
- Ultra-Wide Field Fundus Photos (FP)
- Ultra-Wide Field Fluorescein Angiography (FA)
- OCT Angiography (OU)
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye)

6.2.2 Treatment Period

6.2.2.1 Week 4, Week 8-25 & Week 27-48 (+/- 4 days)

Patients will be followed per the study protocol defined in Section 5.

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Vital Signs
- IOP (pre-dose bilateral)
- SD-OCT (OU)
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye) based on Treatment Group as outlined above

6.2.2.2 Week 26 (+/- 4 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Vital Signs
- IOP (pre-dose bilateral)
- SD-OCT (OU)
- Ultra-Wide Field Fundus Photos (FP)
- Ultra-Wide Field Fluorescein Angiography (FA)
- OCT Angiography (OU)
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye)- depending on treatment interval patients may not receive IAI at this visit

6.2.2.3 End of Study Visit/Early Termination Week 52 (+/- 4 days)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Vital Signs
- IOP (OU)
- SD-OCT (OU)
- Ultra-Wide Field Fundus Photos (FP)
- Ultra-Wide Field Fluorescein Angiography (FA)
- OCT Angiography (OU)
- Indirect Ophthalmoscopy
- Slit Lamp Exam

6.2.3 Early Termination Visit

Patients who are withdrawn from the study should be instructed to return to the clinic for end of study assessments, as described in section 6.2.2.3

6.2.4 Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary, for follow-up of AEs, or for any other reason, as warranted. Procedures performed will be at discretion of evaluating investigator.

6.3 Study Procedures

6.3.1 Procedures Performed only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population.

6.3.2 Efficacy Procedures

6.3.2.1 Best Corrected Visual Acuity

Visual function of the study eye and the fellow eye will be assessed using the 4M ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group 1985) at each study visit, as specified in section 6.1. Visual acuity examiners must be certified to ensure consistent measurement of BCVA, and the examiner should make every effort to remain masked to the patient's previous letter scores and to study eye. A detailed protocol for conducting visual acuity testing and refraction can be found in the visual acuity manual.

6.3.2.2 Fluorescein Angiography/Fundus Photography

The anatomical state of the retinal vasculature of the study eye and the fellow eye will be evaluated by funduscopic examination, FA, and FP at time points according to section 6.1. Photographers will perform FA and FP in both eyes at time points specified in section 6.1. The study eye will be the transit eye. All FA and FP will be archived at the site as part of the source documentation. A detailed protocol for image acquisition and transmission can be found in the imaging manual..

6.3.2.3 Spectral Domain Optical Coherence Tomography

Retinal characteristics will be evaluated using SD-OCT (using a Heidelberg Spectralis, when possible) at time points specified in section 6.1. Images will be captured by OCT technicians using SD-OCT for the study eye and fellow eye. All SD-OCTs will be electronically archived at the study sites as part of the source documentation. A detailed protocol for acceptable OCT machines and SD-OCT image acquisition/transmission can be found in the imaging manual.

6.3.2.4 Optical Coherence Tomography-Angiography (OCT-A)

Retinal vasculature and other disease characteristics will be evaluated using the Optovue Angio-Vue system at time points specified in section 6.1 at sites with capability. OCT angiography has the ability to image vessels based on fluid flow characteristics, and more accurately delineate the vascular layers, it may provide additional information beyond that achievable with the SD-OCT imaging. A detailed protocol for acceptable OCT-A machines and SD-OCT image acquisition/transmission can be found in the imaging manual.

6.3.3 Safety Procedures

6.3.3.1 Vital Signs

Vital signs (blood pressure and heart rate) will be collected at time points specified in section 6.1. Blood pressure will be obtained prior to treatment with IAI with the patient in a sitting position.

6.3.3.2 Intraocular Pressure

Intraocular pressure of both the study eye and fellow eye will be measured at time points specified in section 6.1 using Goldman applanation tonometry or Tono-pen™. Intraocular pressure will be performed bilaterally pre-dose, and in the study eye post-dose.

6.3.3.3 Slit Lamp Examination

The anterior eye structure and the ocular adnexa will be examined using a slit lamp at time points specified in section 6.1.

6.3.3.4 Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed at time points specified in section 6.1; patient's

posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre-dose (bilateral) and post-IAI treatment (study eye) by the investigator. Post-IAI treatment evaluation will be performed immediately after IAI administration.

6.3.3.5 Adverse Event Information Collection

The investigator (or designee) will record all AEs that occur during the study, starting at the time informed consent is signed through week 52, on the AE pages.

The definition of an AE and SAE, and information on the determination of severity and relationship to treatment are provided in section 7.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1 Definitions

7.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient 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 which 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 patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient 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 patient 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 patients source documents and/or CRF. Vital signs will be recorded as AEs only if they are medically relevant.

All AE's and 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 patients. 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 patient signs the informed consent form ("ICF") until 30 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 patient or female partner of a male patient, during the study or within 30 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 patient's withdrawal from the study will be reported to Regeneron Pharmaceuticals, Inc. within 30 days. All SAEs leading to a patient'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

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 patient 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 source documents and/or CRF and/or SAE form, as appropriate.

- **Mild:** Does not interfere in a significant manner with the patient'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 patient.

- **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 patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity will be based on the degree of physiological impairment the value indicates.

-or-

The severity of an AE will be determined by the investigator. The AE will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system, version 3.0 and reported in detail as indicated on the CRF and/or SAE form, as appropriate. Adverse events not listed in the NCI-CTCAE, will be graded according to the following scale:

1 (Mild): Mild AE (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance).

2 (Moderate): Moderate AE (minimal intervention; local intervention; noninvasive intervention [packing, cautery]).

3 (Severe): Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

4 (Life–threatening): Life-threatening or disabling AE (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

5 (Death): Death associated with an AE.

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, weight, height, etc.), disease characteristics including medical history, and medication history for each patient.

8.2 Primary and Secondary Endpoints

The primary endpoint in the study is to assess the safety of 2 mg IAI.

The secondary endpoints are:

- Mean number of IAI received from baseline through week 52
- Resolution of macular edema (mean change in CRT; % patients who achieve a dry macula) at week 52
- Stabilization and improvement in BCVA at week 52
- Percentage of patients avoiding the development of increased neovascularization, vitreous hemorrhage, and need for vitrectomy at week 52.
- Percentage of patients with resolution of retinal hemorrhages, retinal exudates, optic disc edema, capillary non-perfusion at week 52

8.3 Analysis Sets

8.3.1 Efficacy Analysis Sets

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

8.4 Analysis Sets

8.4.1 Efficacy Analysis Sets

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

8.4.2 Safety Analysis Set

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

8.5 Statistical Method

In this study, we will be assessing the effect of aflibercept on vision, retinal anatomy and clinical signs of radiation retinopathy. We will be employing various statistical methods, including a two-group comparison statistical analysis for the following variables: hard exudates, neovascularization, central macular thickness, retinal hemorrhage and best corrected visual acuity (ETDRS). We will employ Chi-square test, Fisher's exact test or 2-proportion z-test for these variables. In addition, ANOVA may possibly be used for group versus assessment period for central macular thickness or best corrected visual acuity.

8.6 Source Document Requirements

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

The investigator will keep all source documents on file. Source documents will be available at all times for inspection by authorized representatives of the regulatory authorities.

9. 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 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.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1 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.

10.2 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 patient 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 patient, in language that he/she can understand. The ICF will be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

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

Patients 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 patient's study record, and a copy of the signed ICF will be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated appropriately. All study patients 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 patient's study record and a copy will be given to the patient.

10.3 Patient Confidentiality and Data Protection

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

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

10.4 Institutional Review Board

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

- The protocol, ICF, and any other materials to be provided to the patients (e.g. advertising) before any patient 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 patients, 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 patients 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.

11. PROTOCOL AMENDMENTS

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

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

12.1 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 patients' interests.

13. STUDY DOCUMENTATION

13.1 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.

13.2 Retention of Records

The investigator will retain all essential study documents, including ICFs, source documents, CRFs, and drug accountability records for at least 15 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.

14. REFERENCES

1. Jampol LM, Moy CS, Murray TG, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first 5 years after brachytherapy. COMS report no. 19. Ophthalmology 2002; 109:2197-206.
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3. Gunduz K, Shields CL, Shields JA, Cater J, Freire JE, Brady LW. Radiation retinopathy following plaque radiotherapy for posterior uveal melanoma. Arch Ophthalmol 1999; 117:609-14.
4. Finger PT, Chin KJ. High-dose (2.0 mg) intravitreal ranibizumab for recalcitrant radiation retinopathy. Eur J Ophthalmol 2013:0.
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7. Finger PT, Mukkamala SK. Intravitreal anti-VEGF bevacizumab (Avastin) for external beam related radiation retinopathy. Eur J Ophthalmol 2011; 21:446-51.
8. Mason JO, 3rd, Albert MA, Jr., Persaud TO, Vail RS. Intravitreal bevacizumab treatment for radiation macular edema after plaque radiotherapy for choroidal melanoma. Retina 2007; 27:903-7.
9. Finger PT. Radiation retinopathy is treatable with anti-vascular endothelial growth factor bevacizumab (Avastin). International journal of radiation oncology, biology, physics 2008;70:974-7.
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11. Gupta A, Muecke JS. Treatment of radiation maculopathy with intravitreal injection of bevacizumab (Avastin). Retina 2008; 28:964-8.

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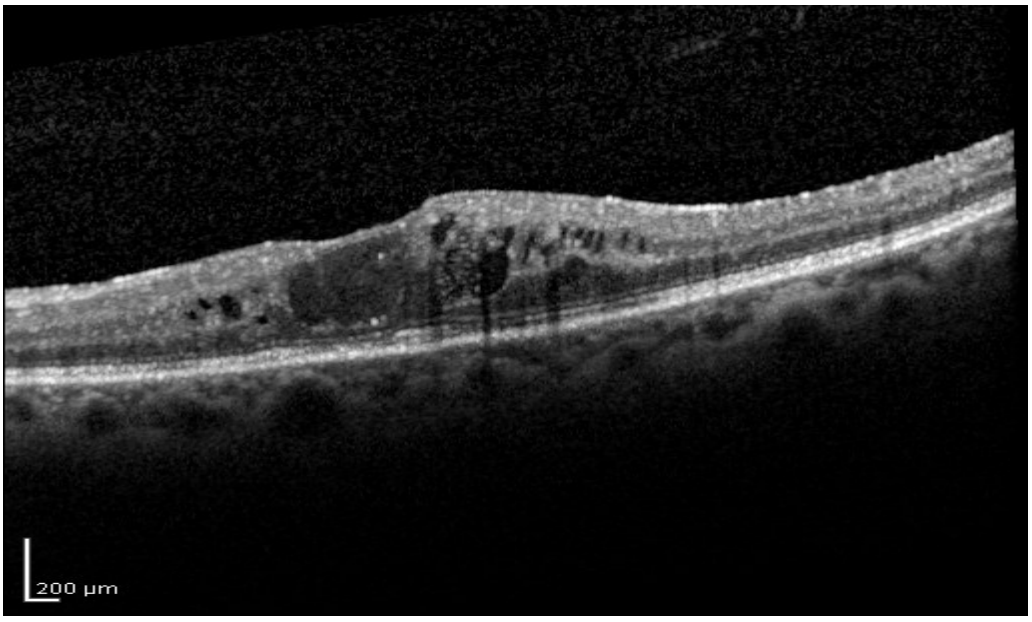
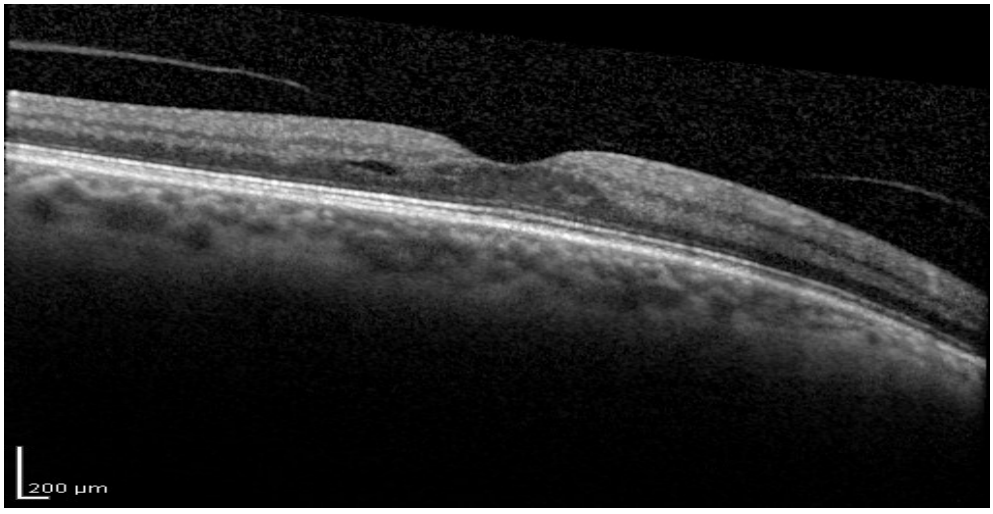
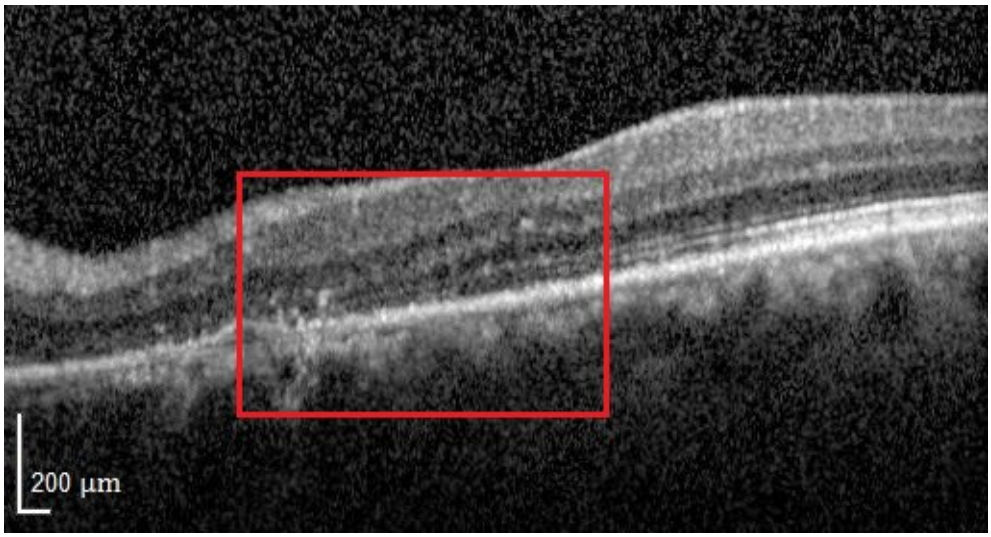
15. APPENDIX I

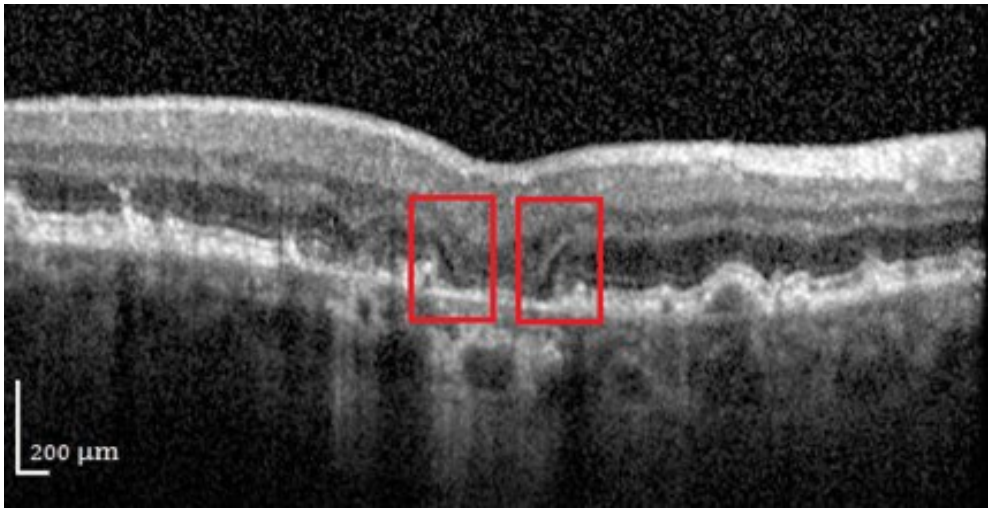
SD-OCT Findings Consistent with Persistent Retinal Edema



SD-OCT Findings Consistent with a dry macula




200 µm


200 µm

16. APPENDIX II

Retinopathy Grading Scale

The severity of intraretinal hemorrhages, hard exudates, and neovascularization in the study eye should be assessed through slit lamp and/or indirect examination by the PI or Sub-Investigator. The PI or Sub-Investigator should grade the severity of intraretinal hemorrhages, hard exudates, and neovascularization based on the grading scale below.

Intraretinal Hemorrhages

The grading scale below is measured by individual hemorrhage. This grading scale should be used to measure the severity of intraretinal hemorrhages in the study eye within the macula.

Grading Scale	Interpretation
0	None
1	0 - 5
2	5 - 10
3	10 - 20
4	➢ 20

Hard Exudates

The grading scale below should be used to measure the severity of hard exudates in the study eye.

Grading Scale	Interpretation
0	None
1	Presence of non-visually significant hard exudate(s)
2	Presence of macular visually significant hard exudate(s)