Clinical Study Protocol

Role of intravitreal aflibercept injection for the treatment of radiation maculopathy

Compound:	Intravitreal aflibercept injection
Study Name:	Role of intravitreal aflibercept injection for the treatment of radiation maculopathy
Clinical Phase:	Phase II, randomized treatment comparing an every six week intravitreal injection arm to a treat and extend arm.
Date of Issue:	15 September 2015
Primary Investigator:	Timothy G. Murray, MD, MBA

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE	Role of intravitreal aflibercept injection for the treatment of radiation maculopathy
SITE LOCATION(S)	Murray Ocular Oncology & Retina, Miami, FL
Principal Investigator	Timothy G. Murray, MD, MBA
OBJECTIVE(S)	To evaluate the benefits of intravitreal aflibercept in patients with visually compromising radiation maculopathy following iodine-125 plaque brachytherapy for uveal melanoma.
STUDY DESIGN	Phase II, randomized treatment comparing an every six week intravitreal injection arm to a treat and extend arm.
STUDY DURATION	54 weeks
ESTIMATED STUDY COMPLETION DATE	September - December 2016
POPULATION	
Sample Size:	Two arms of 25 patients each (totaling 50 patients)
Target Population:	Patients with radiation maculopathy from uveal melanoma treatment (brachytherapy) who have received previous treatment
TREATMENT #1	
Study Drug	Intravitreal aflibercept injection 2 mg
Dose/Route/Schedule:	0.05ml/ 40 mg/mL/Intravitreal Injection every q6 weeks
Treatment #2	
Study Drug	Intravitreal aflibercept injection 2 mg
Dose/Route/Schedule:	0.05ml/ 40 mg/mL/Intravitreal Injection Treat and Extend

ENDPOINT(S)	
Primary:	The primary objective of the study is to assess the safety of intravitreal aflibercept injection in treating visually compromising radiation maculopathy secondary to treatment of uveal melanoma by iodione-125 brachytherapy
Secondary:	The secondary objectives of the study that will be evaluated at the study endpoint include: • Number of injections in control arm compared to TAE arm through week 54 (mean, median, and mode) • BCVA and mean change in BCVA through week 54 • CRT on SD-OCT and mean change in CRT through week 54 • Change in grade and score of radiation maculopathy through week 54 • Change in Qualitative evaluation of FA/ICG at endpoints measured
Exploratory:	• We will assess tumor activity as part of standard of care at each visit. Tumor recurrence/reactivity will be documented.
PROCEDURES AND ASSESSMENTS	This study will consist of 2 simultaneous treatment arms: A six week dosing regimen arm and a treat and extend dosing regimen arm.
STATISTICAL PLAN	Analysis of both sdOCT and visual acuity via t-tests will be performed

1. INTRODUCTION AND RATIONALE

1.1 Introduction

Radiation treatments for uveal melanoma, which include plaque brachytherapy, proton beam radiation, and helium ion radiotherapy, may result in long-term damage to the retinal vascular endothelial cells, causing radiation maculopathy in over 90% of eyes. This damage can be detected and classified through clinical examination, fluorescein angiography, or optical coherence tomography (OCT). OCT classification has gained popularity in the detection and monitoring of radiation-induced maculopathy, and can be graded on a 1–6 scale. This edema grading scale has also been shown to correlate with foveal thickness and visual acuity. Recent findings utilizing spectral domain OCT (SD-OCT) to detect intraretinal cystic spaces and photoreceptor loss have demonstrated that these earliest signs of radiation maculopathy manifest as macular edema, with average onset of OCT-evident edema by 12 months or up to 5 months earlier than clinically detectable radiation maculopathy and as early as 4 months after radiation treatment.

1.2 Rationale

Radiation associated macular edema is a therapeutic challenging. Previous reports suggest that VEGF inhibitors provide a positive anatomic and visual outcome. However, no study to date has evaluated the benefits of intravitreal aflibercept injection in patients with radiation maculopathy.

1.2.1 Rationale for Study Design

The potential reversibility of damage from macular edema can serve as a critical time point for therapeutic intervention. Antivascular endothelial growth factor (anti-VEGF) agents have been proposed for the treatment of radiation-related complications. Furthermore, studies on eyes with uveal melanomas have demonstrated statistically significant increases in the levels of VEGF in both aqueous and vitreous samples compared to eyes without tumors (tumors previously treated with radiotherapy displayed the highest VEGF concentrations). Previous generation anti-VEGF agents, such as

intravitreal bevacizumab, have been effectively used in multiple retinal diseases, including age-related macular degeneration, retinal vein occlusions, diabetic macular edema, and neovascularization. Compared to bevacizumab, newer anti-VEGF agents, such as aflibercept, have been shown to have superior VEGF binding properties, lengthening the time interval between treatments for other retinal conditions; however, there is a lack of data on the effectiveness of intravitreal aflibercept injection in treating radiation maculopathy. Patient follow up will be performed every 6 weeks at a minimum.

1.2.2 Rationale for Dose Selection

Dosing of intravitreal aflibercept injection in the control arm of this study will be within the range of the doses approved by the FDA for other retinal conditions that is known to be safe (2 mg Q4 or Q8Weeks). We expect aflibercept to be at least as effective as other, old anti VEGF agents so the comparator arm will be 2 mg utilizing a treat and extend approach. However, if macular edema increases between follow-up visits, we will shorten the follow-up interval. This interval change will only affect patients in the TAE arm.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to assess the safety of intravitreal aflibercept injection in treating visually compromising radiation maculopathy secondary to treatment of uveal melanoma by iodione-125 brachytherapy.

2.2 Secondary Objective(s)

The secondary objectives of the study that will be evaluated at the study endpoint include:

- Number of injections in control arm compared to TAE arm through week 54 (mean, median, and mode)
- BCVA and mean change in BCVA through week 54

- CRT on SD-OCT and mean change in CRT through week 54
- Change in grade and score of radiation maculopathy through week 54 (see Appendix II – maculopathy grading scale)
- Change in Qualitative evaluation of FA/ICG at endpoints measured

2.3 Exploratory Objective

We will assess tumor activity as part of standard of care at each visit. Tumor recurrence/reactivity will be documented.

3. STUDY DESIGN

3.1 Study Description and Duration:

This study will consist of 2 simultaneous treatment arms: A six week dosing regimen arm and a TAE dosing regimen arm, total duration 54 weeks. In the TAE arm the patients will receive an intravitreal aflibercept injection first visit, again at the second visit at 6 weeks, and then begin treat and extend from second injection forward. Treatment will be given at each visit. We will utilize the radiation maculopathy classification system outlined below. Patients with decreased radiation maculopathy by one grade or more (e.g. from grade 5 to grade 4) will extend re-evaluation by two weeks. Patients with increased radiation maculopathy by one grade or more (e.g. from grade 4 to grade 5) will have re-evaluation decreased by one week (however, we will not decrease follow-up intervals to under four weeks). Patients that show no maculopathy grade change will remain at the same re-evaluation interval. FA/ICG will be completed at baseline, after the 4^{th} injection (or within three weeks of week 24 for the TAE arm), and at the end of the study in all patients. Spectral domain OCT, and clinical evaluation including visual acuity will be assessed every visit in all patients. Radiation maculopathy will be graded every visit in all patients in a blinded fashion using the following classification system: Grade 1 indicates extrafoveal, noncystoid edema; grade 2, extrafoveal cystoid edema; grade 3, foveal noncystoid edema; grade 4, mild-to-moderate foveal cystoid edema; grade 5, severe foveal cystoid edema and grade 6 subretinal fluid. All patients will undergo comprehensive evaluation including adverse event questioning at each study timepoint.

3.2 Patients in the six week dosing arm will receive the last injection at the week 48 visit for a total of 9 intravitreal aflibercept injections during the study. Patients in the TAE treatment group will have variable number of visits resulting in a variable number of injections. A minimum of a four-week follow-up will be required following the last injection for patients in this group. For example, if a patient in the TAE arm demonstrates increased

radiation maculopathy on every visit, their follow up visits will shorten from 6 weeks, to 5 weeks, to 4 weeks, and continue at a q4week interval through the end of the study. Furthermore, if a TAE patient shows decreased radiation maculopathy on every visit, their follow up interval will increase from 6 weeks to 8 week to 10 weeks to 12 weeks to 14 weeks.**Planned Interim Analysis**

Visual acuity OCT outcomes and adverse events will be reviewed at, or around, 24 weeks. Reports of adverse events from this study will be reviewed and summarized periodically while the study is ongoing to ensure the safety of patients.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

This study will consist of 2 simultaneous treatment arms: Both arms will consist of 25 subjects (eyes) for a total of 50, and will span 54 weeks. Patients that withdraw from the study will not be replaced.

4.1 Study Population

Patients over 21 years of age with radiation retinopathy who have received previous treatment will be candidates for the study.

4.1.1 Inclusion Criteria

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

1. 21 years of age and over
2. 20/800 or better visual acuity
3. Must have received previous treatment for radiation maculopathy within the last 4-26 weeks
4. Any presence of macular edema (evaluated by SD-OCT) caused by radiation retinopathy
5. Willing and able to comply with clinic visits and study-related procedures
6. Provide signed informed consent

4.1.2 Exclusion Criteria

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

1. Patients less than 21 years of age.
2. Patients with mental disability or any other condition that precludes the acquisition of an sdOCT image such as (nystagmus, neck disease, etc.)
3. Patients who have previously been treated with intravitreal triamcinolone acetonide for macular edema (signs of recalcitrant disease)
4. Patients who have received anti-VEGF treatments within the last 30 days
5. Current ocular or periocular infection
6. Active intraocular inflammation
7. Any comorbid condition that may decrease visual acuity
8. Any patients who have had intraocular surgery within the past 30 days for any condition
9. Any other condition that the investigator believes would pose a significant hazard to the patient if the investigational therapy were initiated
10. Participation in another simultaneous medical investigation or trial
11. Advanced glaucoma (IOP > 25, even with medications, or cup/disc ratio > 0.8)
12. Pregnant or breast-feeding women
13. Sexually active men* or women of childbearing potential** who are unwilling to practice adequate contraception during the study (adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly). For patients willing to practice adequate contraception during the study, we will recommend that contraception be continued for one month following the last visit
14. Patients that develop anaphylaxis during ICG or FA will be discontinued from the study permanently

*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.

4.2 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, 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 decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. Early termination procedures will be followed.

4.3 Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

This study will consist of 2 simultaneous treatment arms: A six week dosing regimen arm and a treat and extend (TAE) dosing regimen arm. Both arms will consist of 25 subjects (eyes) and will span 54 weeks. Spectral domain OCT, fluorescein angiography, and clinical evaluation including visual acuity will be assessed with sdOCT to determine the presence of intraretinal fluid leakage. All patients will receive intravitreal aflibercept injection 2 mg (0.05ml/ 40 mg/mL).

5.1 Investigational Treatment

This study will investigate if the treat and extend dosing regimen arm has the same effectiveness as treatment every 6 weeks.

5.2 Reference Treatment

Currently, we treat patients every 6-8 weeks with bevacizumab with success. We want to compare the dosing strategy that we have found successful with intravitreal aflibercept injection. The reference treatment in this study will be treatment with intravitreal aflibercept injection every 6 weeks.

5.3 Dose Modification and Stopping Rules

5.3.1 Dose Modification

Dose modification for an individual patient is not allowed.

5.3.1.1 Reasons for Permanent Discontinuation of Study Drug

If a patient develops anaphylaxis or severe intraocular inflammation, the patient will be discontinued from the study permanently. Patients may be permanently discontinued from the study per investigator discretion.

5.3.1.2 Reasons for Temporary Discontinuation of Study Drug

Although the study drug may be discontinued per investigator discretion, no patient will undergo a temporary discontinuation.

5.4 Management of Infusion Reactions

Patients that develop anaphylaxis during ICG or FA will discontinued from the study permanently.

5.4.1 Interruption of the Infusion

Patients having interruption of infusion during ICG or FA will remain in the study.

5.4.2 Termination of the Infusion

Patients having termination of infusion during ICG or FA will remain in the study.

5.5 Method of Treatment Assignment

Patients will be randomly assigned a treatment arm by random number generator with prefixed, sealed envelopes.

5.5.1 Blinding

Blinding will not be undertaken in the study.

5.6 Treatment Logistics and Accountability

5.6.1 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.

5.6.2 Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2° to 8°C to the investigator or designee at regular intervals or as needed during the study. At the end of the study, 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.

5.6.3 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 – or -
- 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.

5.6.4 Treatment Compliance

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

5.7 Concomitant Medications

Patients will not receive any other treatment for macular edema to the study eye other than the study protocol. If a patient needs Anti-VEGF treatment in the non-study eye, intravitreal aflibercept injection will be used as the Anti-VEGF agent throughout the study.

5.7.1 Permitted Medications and Procedure

Patients may undergo cataract and/or vitrectomy during the span of the study. If surgery occurs, intravitreal treatment with triamcinolone acetonide may be used for post-cataract management. Additionally, they will be monitored on post-op day #1, post-op week #1, and post-op month #1. Patients will resume aflibercept treatment 4-6 weeks after surgery.

5.7.2 Prohibited Medications and Procedures

Patients undergoing enucleation will be discontinued from the study.

Concurrent use of systemic or intravenous anti-VEGF agents, intravitreal bevacizumab, ranibizumab or pegaptanib is prohibited.

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

	Screening Period			Treatment Period						
Study Procedure	**Screening And Baseline Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**End of Study Visit 10**
Inclusion/Exclusion	X									
Informed Consent	X									
Medical History	X									
Demographics	X									
Randomization	X									
Administer Study Drug	X	X	X	X	X	X	X	X	X	
IOP assessed	X	X	X	X	X	X	X	X	X	X
Slit Lamp Evaluation	X	X	X	X	X	X	X	X	X	X
SD-OCT Assessment	X	X	X	X	X	X	X	X	X	X
FA/ICG	X			X						X
Fundus Photography	X			X						X
Vital Signs	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X

6.2 Study Visit Descriptions

6.2.1 Screening / Day 1

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:

- Vitals (blood pressure)
- Pregnancy test, if applicable
- ETDRS refraction and best-corrected visual acuity
- IOP assessed
- Slit lamp examination
- Fundus photography
- Fluorescein angiography
- ICG angiography for choroidal tumor vasculature and ischemia
- SD-OCT
- Radiation maculopathy grade/score based on SD-OCT
- Intravitreal aflibercept injection
- Record adverse events

6.2.2 Treatment Period

6.2.2.1 Follow up visits (+/- 3 days)

The following information will be collected:

- Concomitant medications
- Medical and ocular history update
- AEs

The following procedures and assessments will be conducted:

- ETDRS refraction and best-corrected visual acuity
- SD-OCT
- Fundus photography
- Fluorescein angiography *(after 4th injection or within three weeks of week 24 for the TAE arm)*
- ICG angiography *(after 4th injection or within three weeks of week 24 for the TAE arm)*
- Radiation Maculopathy Grade/Score

6.2.3 Last Visit or Termination Visit

All patients will have a mandatory final visit at the end of the study or upon early termination. No study treatment will be administered after the study termination visit.

The following information will be collected at this last visit:

- Concomitant medications
- Medical and ocular history update
- AEs

The following procedures and assessments will be conducted at this last visit:

- Vitals
- ETDRS refraction and best-corrected visual acuity
- Fundus photography
- Fluorescein angiography
- ICG angiography
- SD-OCT
- Radiation maculopathy grade/scale

6.2.4 Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

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 CRF and in the patient's source documents. Laboratory values, vital signs or ECG abnormalities will be recorded as AEs only if they are medically relevant.

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 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 Laboratory, Vital Signs, or Electrocardiogram 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 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 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.

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 patient.

8.2 Primary and Secondary Endpoints

The primary objective of this study is to assess the safety of intravitreal aflibercept injection in treating visually compromising radiation maculopathy secondary to treatment of uveal melanoma by iodine-125 brachytherapy

The secondary objectives of this study are:

- Number of injections in control arm compared to TAE arm through week 54 (mean, median, and mode)
- BCVA and mean change in BCVA through week 54
- CRT on SD-OCT and mean change in CRT through week 54

- Change in grade and score of radiation maculopathy through week 54 (Appendix II)
- Change in Qualitative evaluation of FA/ICG at endpoints measured

The exploratory objective of this study will be to assess tumor activity as part of standard of care at each visit. Tumor recurrence/reactivity will be documented.

9. STATISTICAL PLAN.

9.1 Analysis Sets

We will analyze the total number of patients enrolled and in each arm. Adverse events will be reported for all arms. Visual acuity and SD-OCT analysis will be performed for each group.

9.2 Statistical Methods

9.2.1 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. Descriptive statistics will be used and, when needed, will be acknowledged.

9.2.2 Efficacy Analyses

At each time point mean letter change will be analyzed for all eyes
Number of injections administered will be recorded for each patient
At each time point SD-OCT will be compared to baseline
Analysis of both SD-OCT and visual acuity via t-tests will be performed.
At each time point radiation maculopathy grade/scale will be compared to baseline
FA/ICG/Fundus Photography assessments will be compared to baseline
Tumor progression / reactivation will be assessed and reported as deemed necessary

9.2.3 Safety Analysis

Safety analyses will include all randomized subjects who received any study drug. All AEs will be listed and summarized by treatment group.

Safety and tolerability will be determined by incidence and severity of ocular and systemic adverse events (AEs). Prespecified ocular AEs of interest, identified by ophthalmic examination, are: 6-line loss of VA within the first 3 months of therapy; major subretinal hemorrhage involving ≥ 75% of the clinical macula; disease-related vitreous hemorrhage; injection-related endophthalmitis; retinal detachment or vitreous hemorrhage; and drug-related uveitis. Systemic AEs such as vital sign changes, uncontrolled hypertension, thromboembolic events, hospitalizations, surgeries, emergency department visits, and deaths, will be identified by physical examination, patient reporting, vital sign changes, uncontrolled hypertension, thromboembolic events, hospitalizations, surgeries, emergency department visits, and deaths.

9.2.3.1 Other Safety

Vital Signs

Vital signs (pulse, and blood pressure) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

9.3 Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only safety parameters will be summarized.

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.

11. STUDY MONITORING

11.1 Source Document Requirements

Investigator will prepare and maintain adequate and accurate patient 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.

11.2 Case Report Form Requirements

A CRF for each patient 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 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 a 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.

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

13.4 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 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.

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 patients' 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 3 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. APPENDIX I – INJECTION PROCEDURE

Intravitreal aflibercept injection is formulated as a sterile liquid to a final concentration of 40 mg/mL. The volume of injection will be 50 µl (0.05 mL) for the 2 mg dose of intravitreal aflibercept injection.

The required sequence of steps must be adhered to for administration of the dose in this clinical trial.

- Preparation (please see below regarding the optional use of topical antibiotic agents pre and post dose):
    a. Apply topical anesthetic.
    b. Apply povidone iodine to eyelid margins, eyelashes, and conjunctival surface. For patients who have a known sensitivity to povidone iodine, another equally effective agent may be used.
    c. Place 1 or 2 drops of 5% povidone-iodine on the ocular surface at the intended injection site.
    d. Optional: inject 0.5 mL of 2% xylocaine without epinephrine subjconjunctivally at the intended injection site; (the entry site of the needle for the intravitreous injection should be 3.0-3.5 mm from the limbus in aphakic/pseudophakic patients, and 3.5-4.0 mm in the phakic patients).
    e. Single use Proparacaine bottles should be used for all patients. “Fluoracaine” or other combination Fluorescein Sodium and Proparacaine HCl mixtures should NOT be used.
    f. Apply additional drop of povidone-iodine to site of injection.

- Study Drug Administration:
    a. Insert needle at marked injection point.
    b. Gently inject study drug.
    c. As the needle is withdrawn, a sterile cotton tip applicator should be rolled over the entry site to minimize the risk of drug reflux. This should be held in place for a full 10 seconds.

- Post-Injection Procedures

  Measure patient's IOP before the end of the observation period for each injection. See guidelines below for additional post-injection management procedures.

Guidelines for Pre and Post-injection Management

- Use of Topical Antibiotic Agents

  At the time of this study, the use of topical antibiotics as prophylaxis in IVT injections, both in the preparation and post injection varies considerably between the different practices. There is no consensus on the use of topical antibiotics, the agent to be used and the dose to be administered. In this protocol, it is recommended that a broad-spectrum topical antibiotic be used as part of the preparation for the intravitreal injection procedure, and as prophylaxis in the days immediately following the injection.

  Suggested use:
    - Instruct the patient to self-administer 1-2 drops of the antibiotic to the study eye, 3 times a day, for 3 days before the injection day.
    - On the injection day, as part of the preparation for injection, instill 1 drop to the eye 1 hour before the injection, and another drop 15 minutes before the injection.
    - After the injection, instruct the patient to self-administer 1-2 drops of the topical antibiotic to the injected eye, 3 times a day, for additional 3 days.

- Post-injection reperfusion of the optic nerve

Visualize the optic nerve to verify reperfusion of the central retinal artery in the immediate post-injection period. Verify intravitreal location of therapeutic agent when possible. Verify that the retina is attached and that there is no new intraocular hemorrhage.

- Intraocular pressure

  Monitor intraocular pressure (IOP) before the end of the approximate 30-minute observation period post each injection. Check the IOP while maintaining a clean field. Monitor the IOP closely until it is below 30 mm Hg. If a Tono-pen™ is used to check pressure, a clean Tono-pen™ condom should be placed on the tip before taking each measurement. If Goldmann applanation tonometry is used, the applanator tip should be swabbed with alcohol and let to dry before using it to measure IOP. IOP may be lowered by pharmaceutical or surgical intervention, if required. Treatment should be initiated whenever IOP is increased to the extent that the central retinal artery remains closed and the patient has no light perception for more than 1 to 2 minutes. Transient graying or obscuration of vision following injection, however, is expected and should not be treated.

  Paracentesis should be used only in extreme circumstances when the degree of pressure elevation poses an imminent and irreversible threat to vision. In the rare situation when a paracentesis is warranted, the IOP should be recorded both before and after the procedure. A 0.1 to 0.2 mL paracentesis may be performed at the temporal limbus using a 27-gauge or 30-gauge needle or surgical knife if judged to be necessary by the investigator. Record all IOP measurements in the source document and on the appropriate eCRF page, and related treatments in the concomitant medications section of the source documents and the eCRF.

- Discharge

  No special precautions are required before discharge of a patient who has had an uneventful recovery from intravitreal injection, but patients and/or caregivers should be educated to avoid rubbing the eye and to recognize the signs and symptoms of

endophthalmitis, retinal detachment, or intraocular hemorrhage; these are eye pain or increased discomfort, increased redness of the eye (compared to immediately after injection), blurred or decreased vision, and increased ocular sensitivity to light. Patients should be informed that some blurring of vision is common post-injection, which is often described as seeing spots floating in the eye. The floaters usually resolve after a few days or weeks. Patients who experience post-injection adverse events that require additional monitoring should remain in the clinic for longer than 30 minutes, and treated according to the investigator's medical judgment.

18. APPENDIX II – MACULOPATHY GRADING BY SD-OCT

Spectral domain OCT, and clinical evaluation will be graded every visit in all patients in a blinded fashion using the following classification system:

Grade 1 - indicates extrafoveal, noncystoid edema

Grade 2 - extrafoveal cystoid edema

Grade 3 - foveal noncystoid edema

Grade 4 - mild-to-moderate foveal cystoid edema

Grade 5 - severe foveal cystoid edema and grade 6 subretinal fluid.