

Clinical Study Protocol

Intravitreal aflibercept injection (IAI) for persistent diabetic macular edema (DME) after treatment with bevacizumab and/or ranibizumab (*ROTATED Trial*)

Compound: Aflibercept 2 mg

Study Name: Intravitreal aflibercept injection (IAI) for persistent diabetic macular edema (DME) after treatment with bevacizumab and/or ranibizumab (*ROTATED Trial*)

Clinical Phase: IV

Date of Issue 26 January 2017

Primary Investigator: Dennis Marcus, MD

CLINICAL STUDY PROTOCOL SYNOPSIS

- TITLE:** Intravitreal aflibercept injection (IAI) for persistent diabetic macular edema (DME) after treatment with bevacizumab and/or ranibizumab (*ROTATED Trial*)
- SITE LOCATION(S):** Southeast Retina Center, PC
- PRINCIPAL INVESTIGATOR:** Dennis Marcus, MD
- OBJECTIVE(S):** To evaluate treatment effect of IAI in eyes persistent diabetic macular edema
- STUDY DESIGN:** This is a phase 4 prospective, nonrandomized, open label, interventional clinical trial. Study eyes will receive 5 required initial monthly IAI doses of 2 mg followed by 2q8 IAI for a total of 52 weeks; only one study eye from each patient will be enrolled.
- Starting at week 20 patients may be eligible to receive additional 2mg IAI (2q4) treatment if both of the following criteria is met and the investigator feels additional treatment would be beneficial:
- Loss of >5 letters from baseline or best previously recorded BCVA
 - Presence of new or recurrent intraretinal fluid or subretinal fluid as assessed by SD OCT
- Starting at week 24, rescue therapy with macular laser photocoagulation may be administered if any the following criteria are met
- Loss of > 15 letters from baseline or best previously recorded BCVA and loss of acuity felt to be secondary to DME and not from other cause (i.e., cataract, epiretinal membrane, vitreous hemorrhage, etc) and investigator feels patient would benefit from rescue therapy
 - Increase in SD OCT CSF > 100 um from baseline or best previously recorded SD OCT CSF and investigator feels patient would benefit from rescue therapy.
- Every 4 week visit will include ETDRS BCVA, IOP measurement, Slit lamp biomicroscopy, Indirect ophthalmoscopy, Heidelberg Spectralis SD-OCT and evaluation for systemic and ocular adverse events. Fundus Photography and Wide field Optos fluorescein angiography will be performed at baseline and at week 20 and week 52. For subjects participating in the OCT Angiography sub-study, Optovue OCT angiography will be performed at baseline, weeks 12,20,36, and 52.

STUDY DURATION: Approximately 52 weeks to the end of the study. Primary endpoint will be evaluated at week 52.

EST. COMPLETION

DATE: 2017

POPULATION: 30 patients with persistent DME who have completed and exited the ROTATE trial will be enrolled. Amendment 1 (9 May 2016) was made to expand the inclusion criteria to include additional patients with persistent DME undergoing treatment with bevacizumab and/or ranibizumab beyond those that had been previously enrolled in the ROTATE trial.

TREATMENT(S): Study eyes will receive 5 required initial monthly IAI doses of 2 mg followed by 2q8 IAI for a total of 52 weeks.

This is a phase 4 prospective, nonrandomized, open label, interventional clinical trial. Study eyes will receive 5 required initial monthly IAI doses of 2 mg followed by 2q8 IAI for a total of 52 weeks; only one study eye from each patient will be enrolled.

Starting at week 20 patients may be eligible to receive additional 2mg IAI (2q4) treatment if both of the following criteria is met and the investigator feels additional treatment would be beneficial:

- Loss of >5 letters from baseline or best previously recorded BCVA
- Presence of new or recurrent intraretinal fluid or subretinal fluid as assessed by SD OCT

Starting at week 24, rescue therapy with macular laser photocoagulation may be administered if any the following criteria are met

- Loss of > 15 letters from baseline or best previously recorded BCVA and loss of acuity felt to be secondary to DME and not from other cause (i.e., cataract, epiretinal membrane, vitreous hemorrhage, etc) and investigator feels patient would benefit from rescue therapy
- Increase in SD OCT CSF > 100 um from baseline or best previously recorded SD OCT CSF and investigator feels patient would benefit from rescue therapy.

ENDPOINT(S): Primary:

Reduction in macular edema measured as

- Proportion of eyes with baseline SD OCT CST >350um demonstrating >15% reduction at week 52 from baseline

- Proportion of eyes that demonstrate SD OCT CST <305um (males) and <290 um (females) at week 52 from baseline

Secondary:

- **Vision:**
 - Mean change in BCVA letter score at week 4, week 12, week 20, week 24 and week 52
 - Mean BCVA letter score at week 4, week 12, week 20, week 24, and, week 52
 - Proportion of eyes with any gain (> 0 letters) at week 52, compared to baseline BCVA
- **Anatomic**
 - Mean change SDOCT CSF thickness and macular volume change from baseline at week 4, week 12, week 20, week 24, and, week 52
 - Proportion of eyes with absence of fluorescein angiographic macular leakage at week 52
 - Proportion of eyes with unchanged, worsened or improved fluorescein angiographic macular leakage from baseline at week 20 and week 52
 - Proportion of eyes with unchanged, worsened, or improved fundus photographic DME grading from baseline at week 20 and week 52
 - For patients in the OCT-A substudy:
 - Proportion of eyes with unchanged, worsened, or improved capillary dropout on Optovue OCT Angiography from baseline at week 20 and week 52.
 - Proportion of eyes with unchanged, increased, or decreased macular capillary non-perfusion area of superficial and deep capillary plexus.
 - Mean change in macular capillary non-perfusion area of superficial and deep capillary plexus from baseline at week 12, week 20, week 36, and week 52.
- **Treatment**
 - Mean number of IAI injections from baseline to Week 52
 - Proportion of eyes not requiring rescue therapy from baseline at week 52
- **Safety**
 - Incidence and severity of ocular and systemic safety events through week 52 including: worsened acuity > 30 letters, retinal detachment,

endophthalmitis, cataract progression, vitreous hemorrhage, new PDR or neovascularization of the iris or angle, systemic thromboembolic events, deaths, and systemic serious adverse events.

PROCEDURES/ASSESSMENTS: The following assessments will be conducted at each visit – EDTRS BCVA and SD-OCT. Wide field Optos fluorescein angiography and standard fundus photos will be performed at screening, week 20, and week 52. Adverse events and concomitant medications will be collected at each visit. Subjects participating in the OCT angiography sub-study will have Optovue OCT angiography performed at baseline, weeks 12,20,36, and 52.

STATSITCAL PLAN: This is an open-label study with no formal sample size calculation. Data from all enrolled patients will be analyzed.

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1. INTRODUCTION AND RATIONALE

1.1 Introduction

For the past 25 years, focal/grid laser photocoagulation had been the mainstay of treatment for DME. In the ETDRS, focal/grid photocoagulation of eyes with DME reduced the risk of moderate visual loss by approximately 50% (from 24% to 12%) three years after initiation of treatment. The advent of intravitreal pharmacotherapy with intraocular steroids and anti-VEGF agents have led to numerous clinical trials investigating new therapy for DME.

A study conducted by DRCR.net, A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Focal/grid Photocoagulation for DME (DRCR.net Protocol B), showed triamcinolone as monotherapy was not superior to use with the ETDRS focal/grid laser technique for central-involved DME. Results from a DRCR.net study (“Intravitreal Ranibizumab or Triamcinolone Acetonide in Combination with Laser Photocoagulation for Diabetic Macular Edema”(DRCR.net Protocol I) indicate that treatment for DME with intravitreal anti-vascular endothelial growth factor (anti- VEGF) therapy (0.5 mg ranibizumab) plus deferred (>24 weeks) or prompt focal/grid laser provides visual acuity outcomes at one year and two years that are superior to prompt focal/grid laser alone or intravitreal triamcinolone with prompt focal/grid laser, providing definitive confirmation of the important role of VEGF in DME and the role of anti-VEGF drugs in the treatment of DME. These results with ranibizumab DME therapy were confirmed with other phase 3 trials, including the RISE, RIDE and RESTORE studies. Participants in RISE and RIDE were randomized to continuous monthly 0.5 or 0.3 mg ranibizumab versus sham injections as treatment for DME with macular laser available to all treatment arms. The percentage of individuals gaining > 15 letters from baseline at 24 months was significantly higher in the ranibizumab groups in both studies. In RESTORE, both ranibizumab (0.5mg) monotherapy and combination ranibizumab+laser treatment resulted in better visual acuity outcomes than laser alone in patients with DME. Ranibizumab therapy was well-tolerated in these studies although the overall rate of Antiplatelet Trialists’ Collaboration events was slightly higher in the 0.3 mg (5.6%) and 0.5 mg (7.2%) groups as compared with the sham group (5.2%) in the pooled data from the RISE and RIDE studies. Deaths were also more frequent in the ranibizumab groups (0.8% and 1.6% of sham and 2.4-4.8% of ranibizumab treated patients) in these trials. The rate of non-fatal cerebrovascular events in this pooled analysis was numerically higher in the 0.5mg group (2%) than in the sham (1.2%) or 0.3mg group (0.8%) but the rate of non-fatal myocardial infarctions was similar across treatment groups (2.8%, 2.8% and 2.4% in the sham,

0.3mg and 0.5mg groups, respectively. The results of the RISE and RIDE studies led to the FDA's approval of 0.3 mg ranibizumab for DME and provided anti-vegf therapy as a new standard of care for DME.

Aflibercept is composed of key domains from human VEGF receptors 1 and 2 fused to the Fc domain of human IgG1 and has approximately 100-fold greater binding affinity to VEGF-A than either bevacizumab or ranibizumab. Intravitreal aflibercept injection (IAI; also known in the scientific literature as VEGF Trap-Eye or IVT-AFL) was recently demonstrated to have clinically equivalent efficacy to monthly ranibizumab in neovascular age-related macular degeneration (AMD), whether it was administered monthly or by a more convenient every two months regimen following three initial monthly doses.

The VISTA and VIVID studies are the first phase 3 studies directly comparing VEGF-blockade alone with laser alone in DME. The studies demonstrated mean BCVA gains from baseline to week 52 in the IAI 2q4 and 2q8 groups vs the laser group were 12.5 and 10.7 vs 0.2 letters ($P<0.0001$) in VISTA, and 10.5 and 10.7 vs 1.2 letters ($P<0.0001$) in VIVID. The corresponding proportions of eyes gaining ≥ 15 letters were 41.6% and 31.1% vs 7.8% ($P<0.0001$) in VISTA, and 32.4% and 33.3% vs 9.1% ($P<0.0001$) in VIVID. Similarly, mean reductions in central retinal thickness were 185.9 and 183.1 vs 73.3 μm ($P<0.0001$) in VISTA, and 195.0 and 192.4 vs 66.2 μm ($P<0.0001$) in VIVID. Overall incidences of ocular and non-ocular adverse events and serious adverse events, including the Anti-Platelet Trialists' Collaboration-defined arterial thromboembolic events and vascular deaths, were similar across treatment groups. IAI demonstrated significant superiority in functional and anatomic endpoints over laser at week 52 and these results have led to the recent FDA approval of IAI for DME with 2q8 week dosing after 5 consecutive monthly doses. Thus, IAI dosed every 8 weeks (after 5 initial monthly doses) could provide a therapeutic option that may reduce the total number of injections and necessary office visits, substantially reducing burden on patients, physicians, and the health care system. More recently, DRCR protocol T demonstrated IAI has superior visual acuity outcomes compared to bevacizumab or ranibizumab and bevacizumab for eyes with DME and baseline visual acuity $<20/50$ at 1 year. Central OCT thickness at one year decreased on average by 169 μm (IAI), 147 μm (ranibizumab), and 101 μm (bevacizumab) ($P < .001$ for both IAI vs. Bevacizumab and Ranibizumab vs. Bevacizumab; $P=.036$ for IAI vs. Ranibizumab). At 2 years, among eyes with better baseline VA, DRCR protocol T demonstrated mean VA letter gains of 12.8, 10, and 12.3 from baseline in the IAI, bevacizumab, and ranibizumab groups, respectively. In eyes with poor baseline VA, the mean letter gains at 2 years were 18.3, 13.3, and 16.1 in the IAI,

bevacizumab, and ranibizumab groups, respectively demonstrating IAI superiority over bevacizumab, but no longer over ranibizumab as in year 1. Central OCT thickness at two years decreased on average by 171 μm (IAI), 149 μm (ranibizumab) and 126 μm (bevacizumab) demonstrating superior anatomic improvement via IAI and ranibizumab over bevacizumab ($P < .001$ for IAI vs. Bevacizumab and Ranibizumab vs. Bevacizumab; $P = .26$ for IAI vs. Ranibizumab).

With the above confirmation of the important role and efficacy of anti-VEGF therapy for DME, bevacizumab has evolved to be commonly used as an off-label DME therapy by retina physicians. Bevacizumab has been shown to potentially be efficacious for DME and is low cost and readily available and used by retina physicians.

With FDA approval and availability of IAI for DME, many eyes with persistent DME after bevacizumab and ranibizumab, may be switched to IAI. While previous experience and smaller reports exist for comparing and switching from one anti-VEGF agent to another anti-VEGF agent, there is limited experience with switching from bevacizumab/ranibizumab to the now approved IAI. It is likely that a common clinical scenario for switching from previous bevacizumab/ranibizumab to IAI will occur in eyes with persistent DME or in eyes with resolved DME after frequent anti-vegf injections in an attempt to reduce frequent dosing when recurrent DME occurs. In light of the DRCR T results, IAI may be optimal therapy for persistent DME after previous anti-VEGF therapy.

The DRCR network protocol U has initiated a trial to assess the short-term effects of combination steroid+anti-VEGF therapy on retinal thickness on OCT and visual acuity in comparison with that of continued anti-VEGF therapy alone in pseudophakic eyes with persistent central-involved DME and visual acuity impairment despite previous anti-VEGF treatment. The trial has revised enrollment criteria as recruitment of eligible eyes has been challenging. Thus, prospective and rigorous assessment of alternative therapies in eyes with persistent DME after previous anti- VEGF therapy may be more difficult than anticipated.

We fortunately have a potential population of eyes with persistent DME enrolled in the ROTATE study evaluating the safety and efficacy of 0.3 mg ranibizumab in eyes with persistent DME after recent and frequent bevacizumab (at least 2 bevacizumab injections within 2 months of enrollment and at least 6 bevacizumab injections within 8 months of enrollment). In order to evaluate potential differences in dosing regimens of ranibizumab after previous bevacizumab, eyes were randomized to 12 monthly required injections of 0.3 mg ranibizumab over 1 year or 6 monthly required injections of 0.3 mg ranibizumab for 6 months, followed by PRN dosing (required

ranibizumab if DME persistent on OCT and ETDRS BCVA <20/20) for 6 months. 30 of 30 anticipated eyes have been enrolled. Eyes allocated to both dosing schemes demonstrated improved VA at 1 year, with a mean gain of 6.7 and 6.4 letters in the PRN and Sustained groups, respectively. At month 12, the mean overall decrease in CST thickness was 116 µm overall, with a 92 µm and a 127 µm decrease in the Sustained and PRN groups, respectively. The ocular and systemic safety signals observed were consistent with other anti-VEGF trials in the DME population. These eyes represent a unique cohort for evaluation of IAI in eyes with persistent DME after chronic, recent and frequent anti- VEGF therapy. In addition, the larger, prospective anti-VEGF DME studies such as RISE/RIDE, DRRCR protocol T comparing aflibercept, bevacizumab and ranibizumab, and VIVID/VISTA have required a washout period of at least 3 months without anti-VEGF therapy. Our cohort is unique in that eyes with more recent anti-VEGF therapy can prospectively be evaluated when switched to another anti-VEGF agent.

This cohort provided to opportunity to evaluate if IAI can improve anatomic and visual outcomes in eyes with persistent DME despite previous long-term bevacizumab and/or 0.3 mg or 0.5 mg ranibizumab. In addition, improvement or maintenance of anatomic and visual outcomes will be evaluated with q8weeks dosing with IAI. Given the favorable IAI DRRCR protocol T results at 1 year, as well as trends at year two especially of IAI compared to bevacizumab, evaluation of switching chronic DME eyes to IAI remains important. Amendment I (9 May 2016) was created to expand the inclusion criteria to include additional patients with persistent DME undergoing treatment with bevacizumab and/or ranibizumab beyond those that had been previously enrolled in the ROTATE trial.

1.2 Rationale

1.2.1 Rationale for Study Design

There is limited prospective data evaluating visual and anatomic outcomes in eyes with persistent DME after recent and frequent anti-VEGF therapy. The major DME trials have required lengthy washout periods and may not represent the frequent clinical scenario where switching to a different anti-VEGF agent is considered. Switching to IAI will and is often considered given the results of DRRCR protocol T as well as the less frequent recommended IAI dosing with q8 weeks. The proposed study will provide important data in a prospective manner regarding outcomes when switching to IAI for eyes with recalcitrant DME after frequent and recent bevacizumab and/or ranibizumab.

1.2.2 Rationale for Dose Selection

Phase 3 clinical trials evaluated 2 mg IAI administered every 4 weeks or every 8 weeks for 3 years. Additionally, 2mg IAI has been approved for the treatment of choroidal neovascularization due to age-related macular degeneration, retinal vein occlusion and diabetic macular edema.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the reduction in macular edema measured as:

- Proportion of eyes with baseline SD OCT CST > 350 um demonstrating >15% reduction at week 52 from baseline
- Proportion of eyes with baseline SD OCT CST < 305 um (males) and <290 um (females) at week 52 from baseline.

2.2 Secondary Objectives

The secondary objectives of the study are to evaluate additional efficacy and safety outcomes listed below:

- **Vision:**
 - Mean change in BCVA letter score at week 4, week 12, week 20, week 24, and week 52
 - Mean BCVA letter score at week 4, week 12, week 20, week 24, and, week 52
 - Proportion of eyes with any gain (> 0 letters) at week 52, compared to baseline BCVA
- **Anatomic**
 - Mean change SDOCT CSF thickness and macular volume change from baseline at week 4, week 12, week 20, week 24, and, week 52
 - Proportion of eyes with absence of fluorescein angiographic macular leakage at week 52
 - Proportion of eyes with unchanged, worsened or improved fluorescein angiographic macular leakage from baseline at week 20 and week 52
 - Proportion of eyes with unchanged, worsened, or improved fundus photographic DME grading from baseline at week 20 and week 52
 - For patients in the OCT-A substudy:

- Proportion of eyes with unchanged, worsened, or improved capillary dropout on Optovue OCT Angiography from baseline at week 20 and week 52.
 - Proportion of eyes with unchanged, increased, or decreased macular capillary non-perfusion area of superficial and deep capillary plexus.
 - Mean change in macular capillary non-perfusion area of superficial and deep capillary plexus from baseline at week 12, week 20, week 36, and week 52.
- **Treatment**
 - Mean number of IAI injections from baseline to Week 52
 - Proportion of eyes not requiring rescue therapy from baseline at week 52
 - **Safety**
 - Incidence and severity of ocular and systemic safety events through week 52 including: worsened acuity > 30 letters, retinal detachment, endophthalmitis, cataract progression, vitreous hemorrhage, new PDR or neovascularization of the iris or angle, systemic thromboembolic events, deaths, and systemic serious adverse events.

3. STUDY DESIGN

3.1 Study Description and Duration

This is a phase 4 prospective, nonrandomized, open label, interventional clinical trial. Study eyes will receive 5 required initial monthly IAI doses of 2 mg followed by 2q8 IAI for a total of 52 weeks; only one study eye from each patient will be enrolled.

Starting at week 20, patients may be eligible to receive additional 2mg IAI (2q4) treatment if both of the following criteria is met and the investigator feels additional treatment would be beneficial:

- Loss of >5 letters from baseline or best previously recorded BCVA
- Presence of new or recurrent intraretinal fluid or subretinal fluid as assessed by SD OCT

Starting at week 24, rescue therapy with macular laser photocoagulation may be administered if any the following criteria are met

- Loss of > 15 letters from baseline or best previously recorded BCVA and loss of acuity felt to be secondary to DME and not from other cause (i.e., cataract, epiretinal membrane, vitreous hemorrhage, etc) and investigator feels patient would benefit from rescue therapy

- Increase in SD OCT CSF > 100 um from baseline or best previously recorded SD OCT CSF and investigator feels patient would benefit from rescue therapy.

Panretinal photocoagulation is allowed only for the purpose of treating any new/active proliferative diabetic retinopathy and iris neovascularization.

3.2 Planned Interim Analysis

No interim analysis is planned.

4. SELECTION, WHIDRAWAL, AND REPLACEMENT OF PATIENTS

4.1 Number of Patients Planned

A maximum of 30 patients will be enrolled.

4.2 Study Population

4.2.1 Inclusion Criteria

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

1. Adults \geq 18 years old with Type 1 or Type 2 Diabetes Mellitus
2. Visual acuity letter score in study eye \leq 80 and \geq 20 (approximate Snellen equivalent 20/25 to 20/400)
3. Central-involved DME in study eye (OCT CSF \geq 305 μ m (males) and 290 um (females) on Heidelberg Spectralis spectral domain OCT with evidence of intraretinal or subretinal fluid or cysts).
4. History of at least 6 intravitreal bevacizumab and/or ranibizumab injections within the past 9 months and 2 intravitreal bevacizumab and/or ranibizumab injections within the past 3 months.
5. At least 28 days, but less than 45 days since prior bevacizumab and/or ranibizumab injection
6. No other treatment for DME, other than bevacizumab and/or ranbizumab, in the study eye at any time in the past 3 months (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids or other anti-vegf agents such as macugen)
7. No anticipated major ocular surgery within the next 6 months following randomization.
8. Willing and able to comply with study visits and study-related procedures.

9. Provide signed HIPAA statement and informed consent prior to any study procedures

4.2.2 Exclusion Criteria

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

1. Macular edema considered to be due to a cause other than DME (ERM, Vein Occlusion, Postop CME, uveitis)
2. History of PRP within 3 months prior to enrollment or anticipated need for PRP
3. History of idiopathic or autoimmune uveitis in the study eye
4. Cataract surgery in the study eye within 90 days of baseline
5. Any intraocular surgery within 90 days of baseline
6. Vitreomacular traction or epiretinal membrane in the study eye that is thought to affect vision
7. Clinically significant pre-retinal fibrosis involving the macula in the study eye per investigator judgment
8. Intraocular inflammation of trace or above in the study eye
9. Evidence of active infection in either eye
10. Uncontrolled glaucoma in the study eye defined as a pressure of ≥ 25 on maximal medical therapy.
11. Concurrent disease in the study eye, other than DME, that could compromise VA, require medical or surgical intervention during the study or could confound interpretation of the results
12. Ocular media of insufficient quality to obtain fundus and OCT images
13. Current treatment for a serious systemic infection
14. Administration of systemic anti-angiogenic agents within 180 days of screen
15. History of yag capsulotomy within 1 month prior to enrollment
16. Receipt of any treatment for DME, other than ranibizumab and/or bevacizumab, in the study eye at any time in the past 3 months, (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids or other anti-VEGF agents such as Macugen, any history of 2 mg IAI in the study eye is exclusionary)
17. Any women who are pregnant, breast-feeding, or attempting to become pregnant
18. 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)

*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 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, 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 discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1 Investigational Treatment

The study treatment is 2.0 mg IAI, which will be supplied at a concentration of 40 mg/mL solution for intravitreal injection in a single-use vial. The injection volume will be 50 μ L (0.05 mL) and will be administered to the patients by intravitreal injection.

Study eyes will receive 5 required initial monthly IAI doses of 2 mg followed by 2q8 IAI for a total of 52 weeks.

Starting at week 20 patients may be eligible to receive additional 2mg IAI (2q4) treatment if both of the following criteria is met and the investigator feels additional treatment would be beneficial:

- Loss of >5 letters from baseline or previously best recorded BCVA
- Presence of new or recurrent intraretinal fluid or subretinal fluid as assessed by SD OCT

Starting at week 24, rescue therapy with macular laser photocoagulation may be administered if any the following criteria are met

- Loss of > 15 letters from baseline or best previously recorded BCVA and loss of acuity felt to be secondary to DME and not from other cause (i.e., cataract, epiretinal membrane, vitreous hemorrhage, etc) and investigator feels patient would benefit from rescue therapy
- Increase in SD OCT CSF > 100 um from baseline or best previously recorded SD OCT CSF and investigator feels patient would benefit from rescue therapy.

5.2 Dose Modification and Patient Discontinuation

5.2.1 Dose Modification

Dose modification for an individual patient is not allowed.

5.2.2 Patient Discontinuation

Patients have the right to withdraw from the study at any time for any reason.

The patient may be withdrawn from the study for any of the following reasons: if it is in the best interest of the patient, intercurrent illness, adverse events, or worsening condition. Southeast Retina Center of Dr. Dennis Marcus may request the withdrawal of a patient due to protocol violations, administrative reasons, or any other valid or ethical reason.

If a patient discontinues from the study, they will not be allowed to re-enter the study.

Reasons for patient discontinuation may include, but are not limited to:

- Investigator determination that it is not in the best interest of the patient to continue participation for any reason
- Pregnancy
- Need for alternative therapy in the study eye

- Any serious adverse event
- Safety concerns

5.3 Study Discontinuation

Southeast Retina Center or Regeneron may terminate this study at any time. Reasons for terminating the study include, but are not limited to:

- The incidence or severity of adverse events in this or other studies using intravitreal aflibercept indicating that there is a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete

5.4 Treatment Logistics and Accountability

5.4.1 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.

5.4.2 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 used and unused vials will be returned or disposed of according to Regeneron IST standard operating procedures.

5.4.3 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 inspector's treatment compliance.

5.5 Concomitant Medications

5.5.1 Study Eye

Patients may not receive any medications (approved or investigational) for DME in the study eye other than the assigned study treatment (2 mg IAI) until they have completed the end of the study (week 52) or early termination visit. This includes medications administered locally (eg IVT, topical, juxtasclear, or periorbital routes), as well as those administered systemically, with the intent of treating the study eye and/or fellow eye.

5.5.2 Fellow eye

If a patient requires anti-VEGF therapy in the fellow eye, IAI will be utilized per investigator discretion (IAI provided by Regeneron). Follow-up visits for study eye occur every 4 weeks for 52 weeks. The fellow eye may receive treatment on the same day as the study eye or at an

unscheduled visit but it will not be considered an additional study eye. Safety of the fellow eye will be monitored and all AEs will be collected.

5.5.3 Permitted Medications

Any other medication that are considered necessary for the patient's welfare, and that are not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

Study assessments and procedures are presented below:

Study Procedure	Screening/ Baseline (Day 0)	Weeks 4, 8, 12, 16 (±1 week)	Weeks 20, 24, 28, 32, 36, 40, 48 (±1 week)	Week 52 (±2 weeks) or Early Termination
Review Eligibility Criteria	X			
Review/Sign ICF	X			
Medical History/Demographics	X			
Urine Pregnancy Test (if needed)	X			
HbA1c	X			
Vitals ^a	X	X	X	X
ETDRS BCVA	X	X	X	X
Ophthalmic Exam	X	X	X	X
SD-OCT and Optovue OCT Angiography ^d	X	X	X	X
OPTOS FA and Standard FP	X		X ^b	X
Intravitreal Aflibercept Injection	X	X	X ^c	
Adverse Events/ Con Meds	X	X	X	X

^aBlood pressure, pulse, and respiration rate will be measured after the patient has been sitting for 5 minutes

^bOPTOS (Wide-Field) FA and Standard FP to be performed only at baseline, week 20, and week 52 ^cIAI will be given every 8 weeks at weeks 24, 32, 40, and 48, following administration of the 5 mandatory IAI at screening, weeks 4,8,12, and 16. Additional IAI can be given every 4 weeks beginning at week 20 if protocol defined criteria are met. ^dOptovue OCT Angiography to be performed at baseline, week 12, week 20, week 36, and week 52 only for those subjects participating in the sub-study.

6.1 Study Visit Descriptions

6.1.1 Screening/Baseline (Day 0)

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

- Inclusion/exclusion criteria
- Demographics
- Medical and ophthalmic history and concurrent illnesses
- Concomitant medications

The following procedures and assessments will be conducted:

- HbA1c (HbA1c does not need to be repeated if available in the prior 3 months)
- Urine Pregnancy Test (for women of child bearing potential)
- ETDRS Refraction/BCVA
- Ophthalmic Examination
- Indirect ophthalmoscopy
- SDOCT
- OPTOS (Wide-Field) FA and Standard FP
- Vital signs
- Mandatory Intravitreal Aflibercept Injection
- Optovue OCT Angiography (for sub-study participants only)

6.1.2 Weeks 4, 8, 12, 16 (±1 week)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Ophthalmic evaluation
 - ETDRS Refraction/BCVA
 - Ophthalmic examination
 - Indirect ophthalmoscopy
 - SDOCT
 - Optovue OCT Angiography at week 12 (for sub-study participants only)
 - Vital signs

- Mandatory Intravitreal Aflibercept Injection

6.1.3 Weeks 20, 24, 28, 32, 36, 40, 44, 48 (±1 week)

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Ophthalmic evaluation
 - ETDRS Refraction/BCVA
 - Ophthalmic examination
 - Indirect ophthalmoscopy
 - SDOCT
 - Optovue OCT Angiography at weeks 12, 20, and 36(for sub-study participants only)
 - OPTOS (Wide-Field) FA and Standard FP (week 20)
 - Vital signs
 - Intravitreal Aflibercept Injection:
 - Mandatory IAI will be administered at weeks 24, 32, 40, and 48
 - *Starting at week 20 patients may be eligible to receive additional 2 mg IAI if predefined criteria are met and the investigator feels additional treatment would be beneficial

6.1.4 Week 52 (±2 weeks) or Early Termination

The following Information will be collected

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- Vital signs (Temperature, blood pressure, pulse, and respiration rate will be measured after the patient has been sitting for 5 minutes)
- Ophthalmic evaluation
 - ETDRS Refraction/BCVA
 - Ophthalmic examination
 - Indirect ophthalmoscopy

- SDOCT
- OPTOS (Wide-Field) FA and Standard FP
- Optovue OCT Angiography (for sub-study participants only)

6.1.5 **Unscheduled Visits**

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary at investigator discretion.

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.

Vital sign 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 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:

- 1. Overdose:** Accidental or intentional overdose of the study drug or concomitant medication, whether or not it is considered an AE.
- 2. 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.

These AEs will be reported to:

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

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.

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

7.4 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 (age, race), disease characteristics including medical history and medication history for each patient.

8.2 Primary and Secondary Endpoints

The primary endpoint is the reduction in macular edema as measured by:

- Proportion of eyes with baseline SD OCT CST > 350 um demonstrating > 15% reduction at week 52 from baseline
- Proportion of eyes that demonstrate SD OCT CST < 305 um (males) and <290 um (females) at week 52 from baseline.

The secondary endpoints of the study are listed below:

- **Vision:**
 - Mean change in BCVA letter score at week 4, week 12, week 20, week 24, and week 52
 - Mean BCVA letter score at week 4, week 12, week 24, and, week 52
 - Proportion of eyes with any gain (> 0 letters) at week 52, compared to baseline BCVA

- **Anatomic**
 - Mean change SDOCT CSF thickness and macular volume change from baseline at week 4, week 12, week 20, and, week 52
 - Proportion of eyes with absence of fluorescein angiographic macular leakage at week 52
 - Proportion of eyes with unchanged, worsened or improved fluorescein angiographic macular leakage from baseline at week 20 and week 52
 - Proportion of eyes with unchanged, worsened, or improved fundus photographic DME appearance from baseline at week 20 and week 52
 - For patients in the OCT-A substudy:
 - Proportion of eyes with unchanged, worsened, or improved capillary dropout on Optovue OCT Angiography from baseline at week 20 and week 52.

- Proportion of eyes with unchanged, increased, or decreased macular capillary non-perfusion area of superficial and deep capillary plexus.
 - Mean change in macular capillary non-perfusion area of superficial and deep capillary plexus from baseline at week 12, week 20, week 36, and week 52.
- **Treatment**
 - Mean number of IAI injections from baseline to Week 52
 - Proportion of eyes not requiring rescue therapy from baseline at week 52
- **Safety**
 - Incidence and severity of ocular and systemic safety events through week 52 including: worsened acuity > 30 letters, retinal detachment, endophthalmitis, cataract progression, vitreous hemorrhage, new PDR or neovascularization of the iris or angle, systemic thromboembolic events, deaths, and systemic serious adverse events.

9. STATISTICAL PLAN

This is an open-label study with no formal sample size calculation. Data from all enrolled patients will be analyzed. Reports of adverse events from this study may be reviewed and summarized periodically (anticipated every 24 weeks) while the study is ongoing to ensure the safety of patients.

9.1 Statistical Methods

9.1.1 Demography and Baseline Characteristics

Age, gender, race, HbA1c, number of previous injections, BCVA, OCT thickness, presence or absence of OCT evidence of epiretinal membrane or vitreomacular traction will be collected. OCT thickness and acuity outcomes will be reviewed with ANOVA to assess for any influencing baseline factors.

9.1.2 Efficacy Analysis

9.1.2.1 *Primary Efficacy Analysis-*

Proportions will be determined. Baseline factors and their influences will be evaluated by ANOVA

- Proportion of eyes with baseline SD OCT CST >350 um demonstrating >15% reduction at week 52 from baseline
- Proportion of eyes that demonstrate SD OCT CST <305um (males) and <290 um (females) at week 52 from baseline

9.1.2.2 *Secondary Efficacy Analysis*

Proportions, mean change in ETDRS letters and OCT thickness changes will be determined. Baseline factors and their influences will be evaluated by ANOVA.

- **Vision:**
 - Mean change in BCVA letter score at week 4, week 12, week 20, week 24, and week 52
 - Mean BCVA letter score at week 4, week 12, week 20, and, week 52
 - Proportion of eyes with any gain (> 0 letters) at week 52, compared to baseline BCVA
- *Anatomic: Qualitative analysis/grading will be reviewed by one observer(Principal Investigator) who will compare fundus photos and f/a leakage from baseline to timepoint.*
 - Mean change SDOCT CSF thickness and macular volume change from baseline at week 4, week 12, week 20, and, week 52
 - Proportion of eyes with absence of fluorescein angiographic macular leakage at week 52
 - Proportion of eyes with unchanged, worsened or improved fluorescein angiographic macular leakage from baseline at week 20 and week 52
 - Proportion of eyes with unchanged, worsened, or improved fundus photographic DME appearance from baseline at week 20 and week 52
 - For patients in the OCT-A substudy:
 - Proportion of eyes with unchanged, worsened, or improved capillary dropout on Optovue OCT Angiography from baseline at week 20 and week 52.
 - Proportion of eyes with unchanged, increased, or decreased macular capillary non-perfusion area of superficial and deep capillary plexus.
 - Mean change in macular capillary non-perfusion area of superficial and deep capillary plexus from baseline at week 12, week 20, week 36, and week 52.
- **Treatment**
 - Mean number of IAI injections from baseline to Week 52
 - Proportion of eyes not requiring rescue therapy from baseline at week 52

9.1.3 Safety Analysis

- Incidence and severity of ocular and systemic safety events through week 52 including: worsened acuity > 30 letters, retinal detachment, endophthalmitis, cataract progression, vitreous hemorrhage, new PDR or neovascularization of the iris or angle, systemic thromboembolic events, deaths, and systemic serious adverse events.

9.1.4 Interim Analysis

An interim analysis of the data is not planned.

9.2 Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, outcome measures and safety parameters will be summarized.

10. STUDY MONITORING

10.1 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.

10.2 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.

10.3 AUDITS AND INSPECTIONS

This study may be patient 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 patient 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 patient to inspection.

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

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1 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.

11.2 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.

11.3 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.

11.4 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.

12. PROTOCOL AMMENDMENTS

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

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

13.1 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.

14. STUDY DOCUMENTATION

14.1 Certification of Accuracy Data

The investigator will sign a declaration assuring the accuracy and content of the data recorded on the CRFs. This certification form accompanies each set of CRFs.

14.2 Retention of Records

The investigator will retain all essential study documents, including ICFs, source documents, CRFs, and drug accountability records for at least 5 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.

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16. APPENDIX 1

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 subconjunctivally at the intended injection site; (the entry site of the needle for the intravitreal 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.