Clinical Study Protocol

Investigator Initiated Interventional Study of Subjects With Diabetic Macular Edema Treated With Intravitreal Aflibercept Injection Previously Treated With Other Anti-VEGF Agents.

SWAP-TWO Study

Compound:	Intravitreal aflibercept injection
Study Name:	Study
Clinical Phase:	Phase IV
Date of Issue:	March 28, 2015
Version 6	May 20, 2016

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE	*Investigator Initiated Interventional Study of Intravitreal Aflibercept Injection in Subjects with Diabetic Macular Edema previously treated with Ranibizumab or Bevacizumab.*
TITLE IN LAY TERMS	Treatment of diabetic macular edema with IAI in subjects previously treated with other anti-VEGF agents
SITE LOCATION(S)	
Principal Investigator	Rishi P. Singh, MD Cole Eye Institute Cleveland Clinic Cleveland, Ohio

OBJECTIVE(S)	This interventional study will examine the effects of patients with DME previously treated with other anti-VEGF agents who are transitioned to IAI on a fixed dosing scheme. The following objectives will be evaluated: (1) To assess the efficacy of treatment outcomes by improvements in OCT central subfield thickness and ETDRS visual acuity from baseline (2) To determine safety and tolerability of IAI therapy by monitoring adverse events and (3) To evaluate perfusion changes in OCT angiography including area of nonperfusion and microaneuuersym presence before and after therapy.
STUDY DESIGN	This study is an interventional, single arm, investigator initiated study. Subjects will be given 2 mg (0.05 mL or 50 microliters) of IAI injection administered monthly until OCT demonstrates no evidence of fluid as defined by the protocol, followed by 2 mg (0.05 mL) once every 2 months. Each subject will be evaluated for 12 months. Thus, the study duration will be 12 months plus the recruitment period. Subjects will be evaluated for safety, efficacy as measured by SDOCT and best corrected visual acuity (BCVA) using the Electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) protocol. In additional, fundus photography, fluorescein angiography, and OCT angiography will be performed at baseline, month 6, and at the final visit. Only one eye per subject may be enrolled in the study. If a subject's fellow (non-study) eye requires treatment for at study entry, or during the subject's participation in the study, the fellow eye can receive IAI injection for DME.
STUDY DURATION	12 Months
ESTIMATED STUDY COMPLETION DATE	March 1, 2017
POPULATION	
Sample Size:	20 Subjects
Target Population:	Patients presenting with foveal-involving macular edema

	secondary to diabetes
TREATMENT(S)	IAI injection will be supplied by Regeneron Pharmaceuticals, Inc. and will be administered using standard techniques. Subjects will be given 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every month until OCT demonstrates no evidence of fluid as defined by the protocol followed by 2 mg (0.05 mL) via intravitreal injection once every 2 months.
ENDPOINT(S)	
Primary:	• The primary study endpoint is the mean absolute change from baseline central foveal thickness at month 12 as measured by SDOCT (defined as the average thickness within the central 1mm subfield).
Secondary:	Secondary endpoints would include • The mean change from baseline in best-corrected visual acuity (BCVA) scores at months 6 and 12. • Change in macular OCT perfusion at month 6 and 12 by OCT angiography • The diabetic retinopathy severity changes from baseline at month 6 and 12 as measured by the simplified ETDRS scale. • Presence of microaneurysm and capillary dropout on OCT angiography at month 6 and month 12 by OCT angiography • The percentage of subjects that were anatomically 'dry' by SDOCT at months 6 and 12, • The percentage of participants who gained or lost 5, 10, and 15 letters or more of vision at months 6 and 12 • The percentage of patients that are 20/40 or better at months 6 and 12 • The percentage of patients that are 20/200 or worse at months 6 and 12 • The incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs.

PROCEDURES AND ASSESSMENTS	Ongoing assessments will include BCVA measurement, ophthalmic examinations and recording and evaluation of clinical adverse events. Subjects will undergo SDOCT at each visit. Fundus photography, fluorescein angiography, and OCT angiography will be performed at baseline, month 6, and month 12. Subjects will be given 2 mg (0.05 mL or 50 microliters) IAI administered by intravitreal injection every month until OCT demonstrates no evidence of fluid as defined by the protocol followed by 2 mg (0.05 mL) via intravitreal injection once every 2 months. The fellow eye may also receive IAI as needed for DME as determined by the investigator.
STATISTICAL PLAN	The patients will be compared to their baseline measurement for the primary and secondary outcome. Trends and statistical significant difference will be reported.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
CRF	Case report form
EC	Ethics Committee
eCRF	Electronic case report form
FAS	Full analysis set
ICF	Informed consent form
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event

1. INTRODUCTION AND RATIONALE

1.1 Introduction

DR is a major cause of blindness among American adults aged 40 years and older. The prevalence of DR in this population is increasing; it currently affects 4.2 million people, and it is projected that this figure will rise to 6 million people by the year 2020. Vision-threatening diabetic retinopathy (VTDR) is estimated to affect 700,000 individuals in the US. By 2020, this is expected to increase to 1.34 million people. Diabetic macular edema (DME) is the most common cause of vision loss from diabetic retinopathy. It is characterized by macular swelling secondary to increased vascular permeability secondary to loss of pericytes in the macular vascular bed. Clinically, microaneurysms and exudates are often seen in association with macular edema. Foveal-involving cystic changes and macular edema can have significant impact on visual loss. Extent of perfusion and ischemia also is important for visual prognosis.

Multiple factors play a role in the evolution of diabetic macular edema. Vascular endothelial growth factor has been shown to be significantly elevated in diabetic retinopathy and may play an important role in the evolution and pathogenesis of DME. Increasing VEGF levels are also seen in the setting of progressive ischemia, such as proliferative diabetic retinopathy when extensive peripheral nonperfusion may be present (Wessel et al, 2012). Additionally significant peripheral vascular perfusion abnormalities are often seen in other retinal vascular diseases (Singer et al, 2014). Reducing the active levels of VEGF may have significant positive consequences for outcomes related to DME. VEGF has 2 properties that explain its important roles in normal fetal development and in biology: VEGF is a powerful mitogen for endothelial cells (Ferrara et al., 1991), thus promoting formation of new vessels that are required for normal and pathological tissue growth (Ferrara, 2000; Ferrara and Davis-Smyth, 1997).

VEGF is a homodimeric protein with a molecular weight of 34 to 42 kDa (Thickett, 1999). VEGF binds to and activates 2 high affinity receptors, Flt-1 (VEGFR1) and Flk-1 (VEGFR2), which are predominantly located on the vascular endothelium.

IAI is a recombinantly produced fusion protein consisting of portions of the human VEGF receptor extracellular domains fused to the Fc domain of human IgG1 (Figure 1). IAI is comprised of portions of the extracellular domains of 2 different VEGF receptors. It contains sequences encoding Ig domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the hinge region of the human IgG1 Fc domain. IAI is a dimeric glycoprotein with a protein molecular weight of 97 kDa, and contains ~15% glycosylation to give a total molecular weight of 115 kDa.

Figure 1. The IAI Molecule

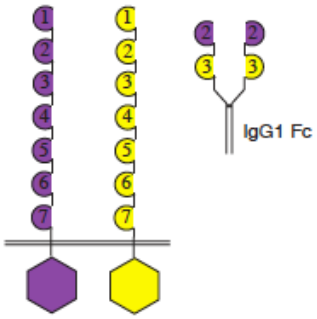

Figure 1. VEGFR1 and VEGFR2 are related receptors that have 7 Ig domains in the extracellular portion and a tyrosine kinase domain intracellularly. IAI contains the VEGFR1 Ig2 domain fused to the VEGFR2 Ig3 domain, which is in turn fused to the IgG1 Fc.

IAI has several potential advantages over other VEGF blockers: it has a much higher affinity (~ 0.5 pM dissociation constant for VEGF165 and VEGF121) than a humanized monoclonal antibody. IAI also binds the related factors Placental Growth Factor 1 and 2 (PLGF1 and PLGF2), which may be advantageous in certain disease situations, including retinal neovascularization (Rakic et al 2003).

1.2 Rationale

1.2.1 Rationale for Study Design

Multiple phase III studies (e.g., RISE, RIDE, VISTA, VIVID,), have evaluated intravitreal anti-VEGF agents for the management of DME. Results from these studies demonstrated clinical efficacy and significant improvements in visual acuity and macular thickness. There are three currently utilized anti-VEGF agents for DME used: bevacizumab (Avastin, Genentech/Roche), ranibizumab (Lucentis, Genentech/Roche), and aflibercept (Eylea, Regeneron/Bayer).

A head to head comparison of these agents was recently completed. Protocol T was a multicenter, randomized clinical trial comparing the efficacy and safety of aflibercept 2.0 mg, bevacizumab 1.25 mg, and ranibizumab 0.3 mg in patients with type 1 or type 2 diabetes and with at least 1 eye with center-involved DME and no anti-vascular endothelial growth factor (anti-VEGF) treatment within 12 months prior to enrollment (N=660). The mean duration of diabetes was 17 years; the mean visual acuity (VA) at baseline was approximately 20/50 (Table 1). A little more than a third of patients had prior focal/grid laser photocoagulation and 11% to 14% had prior anti-VEGF therapy for DME.

Treatment was every 4 weeks while the eye was improving or worsening. Treatment was deferred when VA was 20/20 or better, with central subfield thickness (CST) below the eligibility threshold (250 µm to 320 µm) or the eye was stable for 2 injections (Figure 1). The mean improvement in VA letter score was greater with aflibercept than with bevacizumab (13.3 vs. 9.7; *P*<.001) or ranibizumab (13.3 vs. 11.2; *P*=.03). The relative effect varied according to initial VA,

with the mean improvement from baseline increasing with worse initial VA letter score (<69; 20/50 or worse at baseline). In this subpopulation (49% of cohort), mean improvement was +18.9 for aflibercept, +11.8 for bevacizumab, and +14.2 for ranibizumab. The median number of injections (maximum possible 13) was 9 for aflibercept, 10 for bevacizumab, and 10 for ranibizumab. Laser photocoagulation, at least once between 24 and 48 weeks, was performed in 36% of aflibercept-treated eyes, 56% of bevacizumab-treated eyes, and 46% of ranibizumab-treated eyes (*P*<.001 for overall comparison). Retinal thickening was decreased to <250 μm in 66% of aflibercept-treated eyes, 36% of bevacizumab-treated eyes, and 58% of ranibizumab-treated eyes. Bevacizumab was statistically significantly less effective for improving CST outcomes than either aflibercept or ranibizumab.

While all treatments demonstrated significant treatment benefit, there were clearly differences in the anti-VEGF agent and the anatomical and vision response in patients especially in those with vision 20/50 or worse. Complicating matters further, Protocol T does not reflect the general population of patients under treatment under retina practices. Protocol T required patients to not have anti-VEGF therapy for a minimum of 12 months prior to entry. Thus, there is a gap in understanding on what the outcomes will be when patients are transitioned to IAI from other therapies.

In addition, the majority of retina specialists also do not treat on a fixed dosing pattern as seen in registration trials and instead employ a pro re nata (PRN) treatment regimen based on OCT and clinical exam. Does the movement from PRN treatments to a fixed dosing scheme of every 2 months achieve the same visual and anatomical outcomes?

Below is the schema for retreatment in Protocol T. Because of the complexity of the treatment algorithm, the treatment frequency from protocol T would not likely be adopted to retina practices. Therefore a regimen with a fixed dosing interval may improve clinical efficiency and decrease clinical visits for patients with DME.

Preliminary studies have suggested that there is a significant amount of retinal vascular changes (e.g., increased permeability, ischemia) in patients with DME ((Wessel et al, 2012). These global assessments of OCT angiographic features, including leakage and ischemia, may allow for a better characterization of the disease burden and allow for the development of imaging biomarkers that have implications for therapeutic response or resistance. This study will prospectively assess the alterations in OCT angiographic parameters to provide insights into the retinal vascular changes that occur during treatment with IAI and to examine the relationship between these features and treatment response.

1.2.2 Rationale for Dose Selection

The dose and treatment regimen was selected based on the phase III studies and the drug package insert. Specifically, subjects will be given 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every month until OCT demonstrates no evidence of fluid as defined by the protocol, followed by 2 mg (0.05 mL) via intravitreal injection once every 2 months.

2. STUDY OBJECTIVES

2.1 Primary Objective

- The primary study endpoint is the mean absolute change from baseline central foveal thickness at month 12 as measured by SDOCT (defined as the average thickness within the central 1mm subfield).

2.2 Secondary Objective(s)

- To assess the efficacy of treatment outcomes by improvements in ETDRS visual acuity from baseline
- To determine safety and tolerability of IAI therapy by monitoring adverse events.
- To determine perfusion changes in OCT angiography including area of nonperfusion and microanuersym presence before and after therapy.

STUDY DESIGN

2.3 Study Description and Duration

Subjects will be assigned to treatment with 2 mg IAI (0.05 mL or 50 microliters) administered monthly until OCT demonstrates no evidence of fluid as defined by the protocol, followed by 2 mg (0.05 mL) once every 2 months.

The planned enrollment for the 20 subjects needed for this study is estimated to be 12 months. The study duration for each subject is scheduled to be 12 months.

Only one eye will be designated as the study eye. For subjects who meet eligibility criteria in both eyes, the investigator and patient will select the study eye.

Subjects will be evaluated at Cole Eye Main Campus for Screening/Baseline, Visit Month 6 and Visit Month 12. All other visits may occur at Twinsburg Family Health Center- Ophthalmology or Strongsville Family Health Center- Ophthalmology if that office suits the subject travel needs.

2.4 Study Committees

Appropriate action, if needed, will be taken based upon this review and in consultation with the principal investigator. All events will be managed and reported in compliance with all applicable regulations and included in the final clinical study report.

3. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

3.1 Number of Subjects Planned

The target enrollment for this study is 20 subjects.

3.2 Study Population

Subjects will be recruited through clinics at the Cole Eye Institute, Cleveland OH. The study will seek approval from the Cleveland Clinic Investigational Review Board (IRB) and all study related procedures will be performed in accordance with the Declaration of Helsinki and US Code 21 of Federal Regulations.

3.2.1

Inclusion Criteria

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

1. Signed Informed Consent.
2. Men and women ≥ 18 years of age.
3. Foveal-involving retinal edema secondary to DME based on investigator review of clinical exam and SDOCT with central subfield thickness value of 325 microns by Zeiss Cirrus SD-OCT.
4. E-ETDRS best-corrected visual acuity of: 20/25 to 20/400 in the study eye.
5. History of previous treatment with anti-VEGF with at least 4 injections over the last 6 months.
6. Willing, committed, and able to return for ALL clinic visits and complete all study related procedures.
7. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Exclusion Criteria

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

1. Any prior or concomitant therapy with another investigational agent to treat DME in the study eye.
2. Prior panretinal photocoagulation in the study eye within the past 3 months.
3. Prior intravitreal anti-VEGF therapy in the study eye within 30 days of enrollment.
4. Prior Flucinolone implantation (Iluvein) or prior Ozurdex within 6 months of study entry. Prior intravitreal steroid within 4 months of study entry.
5. Prior systemic anti-VEGF therapy, investigational or FDA-approved, is only allowed up to 3 months prior to first dose, and will not be allowed during the study.

6. Previous treatment with intravitreal aflibercept injection
7. Significant vitreous hemorrhage obscuring view to the macula or the retinal periphery as determined by the investigator on clinical exam
8. Presence of other causes of macular edema, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, choroidal neovascularization, age-related macular degeneration or multifocal choroiditis in the study eye. Epiretinal membranes are not considered an exclusion. .
9. Presence of macula-threatening traction retinal detachment.
10. Prior vitrectomy in the study eye.
11. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
12. Any history of macular hole of stage 2 and above in the study eye.
13. Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as it's unlikely to interfere with the injection.
14. Uncontrolled glaucoma at baseline evaluation (defined as intraocular pressure ≥25 mmHg despite treatment with anti-glaucoma medication) in the study eye.
15. Active intraocular inflammation in either eye.
16. Active ocular or periocular infection in either eye.
17. Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye.
18. Any history of uveitis in either eye.
19. History of corneal transplant or corneal dystrophy in the study eye.
20. Significant media opacities, including cataract, in the study eye which might interfere with visual acuity, assessment of safety, or fundus photography.
21. Any concurrent intraocular condition in the study eye (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the 52 week study period.
22. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the subject beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety.
23. Participation as a subject in any clinical study within the 12 weeks prior to Day 1.

24. Any systemic therapy with an investigational agent in the past 3 months prior to Day 1.
25. Any history of allergy to povidone iodine.
26. Pregnant or breast-feeding women
27. 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)

*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.

3.3 Premature Withdrawal from the Study

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

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

Should a subject (or a subject's legally authorized guardian or representative) decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. Early termination procedures should be followed, as delineated in section 5.2.4.

3.4 Replacement of Subjects

Subjects prematurely discontinued from the study will not be replaced.

4. STUDY TREATMENTS

Subjects will be initially assigned to treatment with 2 mg intravitreal IAI injection (0.05 mL or 50 microliters) administered monthly until OCT demonstrates no evidence of fluid as defined by the protocol, followed by 2 mg (0.05 mL) once every 2 months.

No evidence of fluid is defined as:

1. Lack of subretinal fluid
2. Central subfield thickness of less than 300 microns
3. Grade 2 or lower CME grade. CME grade is defined as:
    a. Grade 0: no CME
    b. Grade 1: extrafoveal CME or foveal depression present
    c. Grade 2: foveal CME with fovea flat

d. Grade 3: CME with fovea slightly raised
e. Grade 4: CME with fovea significantly raised

4.1 Additional Treatment

Additional treatment with IAI can be applied if the subject experiences any of the following events since the last treatment:

- Loss of 15 or more ETDRS letters from best previous measurement AND increase in 75 microns of retinal thickness as compared to the last previous visit.

If the subject meets additional treatment criteria, the subject will be switched to monthly visits and assessments.

4.2 Dose Modification and Stopping Rules

4.2.1 Dose Modification

Dose modification for an individual subject is not allowed.

4.2.2 Study Drug Stopping Rules

Information on follow-up for subjects who permanently discontinue from study drug, but choose to remain in the study is provided in section 6.2.4.

4.3 Method of Treatment Assignment

All subjects are enrolled in the same cohort to receive treatment with intravitreal aflibrecept injection.

4.3.1 Blinding/Masking

This is a single arm treatment study and the patients and physicians will be aware of their current treatment assignment and schema.

4.3.2 Packaging, Labeling, and Storage

2.0 mg intravitreal IAI injection is formulated as a sterile liquid to a final concentration of 40 mg/mL intravitreal IAI injection in 5% sucrose, 10 mM sodium phosphate pH 6.3, 0.03% polysorbate 20, and 40 mM NaCl. Intravitreal IAI 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 0.05 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.

4.3.3 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.

4.3.4 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.

4.3.5 Treatment Compliance

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

4.4 Concomitant Medications and Procedures

Study Eye:

Subjects may not receive any medications (approved or investigational) for their DME in the study eye other than the assigned study treatment (intravitreal IAI injection as specified in this protocol, until they have completed the end of study (12 months) or ET visit assessments. This includes medications administered locally (e.g., IVT, topical, juxtascleral or periorbital routes), as well as those administered systemically, with the intent of treating the study and/or fellow eye. No focal/grid laser photocoagulation can be performed during the study. Panretinal laser photocoagulation can be performed for the presence of proliferative disease with vitreous hemorrhage or other high risk characteristics (e.g., neovascularization of the disc) during the course of the study.

Fellow Eye:
If a subject's fellow (non-study) eye requires treatment for DME study entry, or during the subject's participation in the study, the fellow eye can receive IAI. Intravitreal aflibercept injection will be provided at no cost by Regeneron for the fellow eye. Although the fellow eye can receive treatment, it will not be considered an additional study eye. The fellow eye may also receive laser photocoagulation, as needed, at investigator discretion.

4.4.1 Permitted Medications and Procedures

Any other medication that are considered necessary for the subject'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.

4.4.2 Prohibited Medications and Procedures

Systemic anti-angiogenic agents will not be permitted during the study. Patient must refrain from the use of oral or topical steroids for 12 months during the course of the study. Patients must also refrain from the use of topical nonsteriodal agents, system nonsteroidal agents, intraocular anti-VEGF agents, and systemic anti-VEGF agents for 12 months during the course of the study for treatment of the study eye.

4.5 Post-Study Treatment

All medications are permitted post-study treatment.

5. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

5.1 Schedule of Events

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

Table 1 Schedule of Events

Study Procedure	Treatment Period (Visit intervals after baseline are 28 days since last visit +/- 7 days)													Additional
	Screening & Baseline Visit 1	2	3	4	5	6	7*	8	9*	10	11*	12	End of Treatment Visit 13	Unscheduled Follow up Visit or Early Termination
Day/Month	Month 0	M 1 28 days +/- 7 days	M 2 28 days +/- 7 days	M 3 28 days +/- 7 days	M 4 28 days +/- 7 days	M 5 28 days +/- 7 days	M 6 28 days +/- 7 days	M 7 28 days +/- 7 days	M 8 28 days +/- 7 days	M 9 28 days +/- 7 days	M 10 28 days +/- 7 days	M 11 28 days +/- 7 days	Month 12 +/-10 days	NA
Inclusion/Exclusion	x													
Informed Consent	x													
Medical History Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	
Demographics	x													
ETDRS Manifest Refraction/Slit Lamp/Tonometry/ Fundus Exam study eye	x	x	x	x	x	x	x	x	x	x	x	x	x	x
OCT angiography	x						x						x	
SDOCT study eye	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ultra Wide Field Fluorescein Angiography**	x						x						x	
Ultra Wide Field Fundus Photography	x						x						x	
Administer Study Drug (intravitreal IAI injection)*	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x

* IAI will be given monthly until there is no evidence of fluid is defined as: 1. Lack of subretinal fluid 2. Central subfield thickness of less than 300 microns, 3. Grade 2 or lower CME grade as defined in section 4.0. If subject meets additional treatment requirements as defined in section 4.1 of the protocol, the patient will be treated in q1 intervals.

** In cases of fluorescein dye intolerance with severe allergic reaction, patient may be excluded from this evaluation.

5.2 Study Visit Descriptions

5.2.1 Screening/Baseline Visit, Day 0,

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

- Inclusion/exclusion
- Informed consent documentation
- Demographics
- Medical history and concurrent illnesses
- Concomitant medications

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination (Including IOP measurement)
- Fundus examination
- Spectral Domain OCT evaluation
- Ultra Wide Field Fundus photography
- Ultra Wide Field Fluorescein angiography
- OCT angiography evaluation
- Intravitreal aflibercept injection

5.2.2 Follow-up Periods

5.2.2.1 Q1 month interval visit (+/- 7 Days)-month 6 and 12 are mandatory visits and additional tests are listed below

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination (including IOP measurement)
- Fundus examination
- Spectral Domain OCT evaluation
- Ultra Wide Field Fundus Photography (month 6 and 12 only)

- Ultra Wide Field Fluorescein angiography (month 6 and 12 only)
- OCT angiography (month 6 and 12 only)
- Intravitreal aflibercept injection (if deemed necessary based on OCT)

5.2.2.2 Early Termination visit

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination (including IOP measurement)
- Fundus examination
- Spectral Domain OCT evaluation

5.2.3 Additional Visits

5.2.3.1 Unscheduled visit

The following information will be collected:

- Concomitant medications
- AEs

The following procedures and assessments will be conducted:

- ETDRS visual acuity with manifest refraction
- Slit lamp examination (including IOP measurement)
- Fundus examination
- Spectral Domain OCT evaluation

5.2.4 Early Termination Visit

Subjects who are withdrawn from the study should be instructed to return to the clinic for end of study assessments.

5.2.5 Unscheduled Visits

All attempts should be made to keep subjects on the study schedule. Unscheduled visits may be necessary to repeat testing following AEs, or for any other reason, as warranted.

5.3 Study Procedures

5.3.1 Procedures Performed only at the Screening/Baseline Visit

No specific procedures other than above will be performed for the sole purpose of determining study eligibility or characterizing the baseline population.

5.3.2 Efficacy Procedures

Vision: Visual Acuity Visual function of the study eye and the fellow eye will be assessed using the E-ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985). Visual Acuity examiners must be certified to ensure consistent measurement of BCVA.

Spectral Domain Optical Coherence Tomography (OCT): Retinal characteristics will be evaluated using SDOCT on the study eye. At the Screen Visit (Visit 1) images will be captured and archived. The scanning protocol will consist of fast macular thickness maps as well as high definition 6.0 mm linear scans centered on the fovea. OCT scans will be recorded by scoring their morphological patterns, and by recording the foveal minimum and volumetric analysis for each subject (Cirrus OCT, Humphrey Zeiss Inc., San Leandro, CA, software version 5.0). OCT images will read by a trained reader and also assessed with a computerized segmentation analysis tool.

Spectral domain optical coherence tomography (OCT) is noninvasive noncontact imaging technique that is among the most commonly ordered diagnostic tests in ophthalmology. OCT allows for high-resolution visualization of eye structures including the retina, choroid, and optic nerve. OCT technology uses light in a similar method to ultrasound.

OCT angiography (OCT-A) utilizes OCT technology and special software to reconstruct the active vascular network in the area of interest. This is a major breakthrough in technology because for the first time a clinician has the ability to visualize the perfused vascular network in a noninvasive and minimal risk way.

OCT-A software is now available on various FDA-cleared OCT devices. The software is currently not FDA-approved as the clinical endpoints have not been defined and normative validation has not been completed. (see rationale for exemption for IDE in research procedures below). Utilizing OCT-A software does not impact the patient. Following obtaining the OCT image with the FDA-approved system, the OCT-A software is then used to process sequential OCT scans to reconstruct the vascular network. Although this software is not approved for use in the United States, it presents minimal risk to the patient and the procedure for imaging is exactly the same as that of spectral-domain OCT.

The data obtained from OCT-A may provide important information on disease activity.

Fundus Evaluation, Fundus Photography, and Fluorescein Angiography (FA):
The anatomical state of the retinal vasculature of the study eye will be evaluated by funduscopic examination. Ultra-widefield fundus photography and fluorescein angiography will be performed at the baseline visit, month 6, and at the month 12 visit. OCT angiography will be performed at the baseline visit, month 6, and at the month 12 visit. Angiographic analysis will be performed by a trained reader and a computerized analysis tool.

Intraocular Pressure:
Intraocular pressure (IOP) of the study eye will be measured using applanation tonometry or Tonopen. The same method of IOP measurement must be used in each subject throughout the study.

5.3.3 Safety Procedures

5.3.3.1 Adverse Event Information Collection

The investigator (or designee) will record all AEs that occur during the study following the baseline visit. Information on follow-up for AEs is provided in section 6.2.4.

The definition of an AE and SAE, and information on the determination of severity and relationship to treatment are provided in section 6.

6. SAFETY DEFINITIONS, REPORTING, AND MONITORING

6.1 Definitions

6.1.1 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.

6.1.2 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.

6.2 Recording and Reporting Adverse Events

All AEs and SAEs will be recorded in the patient's source documents. Laboratory values or vital signs 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 subjects. This includes death from any cause and all SAEs related to the use of the study drug. All SAEs will be reported to the IRB, regardless of assessed causality.

6.2.1 Deaths

Any AE that results in death is considered a 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

6.2.2 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

6.2.3 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

6.2.4 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.

6.3 Evaluation of Severity and Causality

6.3.1 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.

6.3.2 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.

7. STUDY VARIABLES

7.1 Demographic and Baseline Characteristics

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

7.2 Primary and Secondary Endpoints

Primary Endpoint:

- The primary study endpoint is the mean absolute change from baseline central foveal thickness at month 12 as measured by SDOCT (defined as the average thickness within the central 1mm subfield).

Secondary Endpoint:

Secondary endpoints would include

- The mean change from baseline in best-corrected visual acuity (BCVA) score at months 6 and 12.
- Change in macular OCT perfusion at month 6 and 12 by OCT angiography
- The diabetic retinopathy severity change from baseline at month 6 and 12 as measured by the simplified ETDRS scale.
- Presence of microaneurysm and capillary dropout on OCT angiography at month 6 and month 12 by OCT angiography
- The percentage of subjects that were anatomically 'dry' by SDOCT at months 6 and 12
- The percentage of participants who gained or lost 5, 10, and 15 letters or more of vision at months 6 and 12
- The percentage of patients that are 20/40 or better at months 6 and 12
- The percentage of patients that are 20/200 or worse at months 6 and 12
- The incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs.

7.3 Analysis Sets

7.3.1 Efficacy Analysis Sets

The full analysis set (FAS) includes all subjects who received any study drug. Efficacy endpoints will be analyzed using the FAS.

7.3.2 Safety Analysis Set

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

7.4 Subject Disposition

The following will be provided:

- The total number of enrolled subjects
- The total number of subjects who discontinued the study, and the reasons for discontinuation
- A listing of subjects prematurely discontinued from treatment, along with reasons for discontinuation

7.5 Statistical Methods

7.5.1 Demography and Baseline Characteristics

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

7.5.2 Efficacy Analyses

7.5.2.1 Primary Efficacy Analysis

- The primary study endpoint is the mean absolute change from baseline central foveal thickness at month 12 as measured by SDOCT (defined as the average thickness within the central 1mm subfield).

7.5.2.2 Secondary Efficacy Analysis

Secondary efficacy variables include the following:

- The mean change from baseline in best-corrected visual acuity (BCVA) score at months 6 and 12.
- Change in macular OCT perfusion at month 6 and 12 by OCT angiography

- The diabetic retinopathy severity change from baseline at month 6 and 12 as measured by the simplified ETDRS scale.
- Presence of microaneurysm and capillary dropout on OCT angiography at month 6 and month 12 by OCT angiography
- The percentage of subjects that were anatomically 'dry' by SDOCT at months 6 and 12
- The percentage of participants who gained or lost 5, 10, and 15 letters or more of vision at months 6 and 12
- The percentage of patients that are 20/40 or better at months 6 and 12
- The percentage of patients that are 20/200 or worse at months 6 and 12
- The incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs.

7.5.3 Safety Analysis

7.5.3.1 Adverse Events

Definitions

For safety variables, two observation periods are defined:

- The treatment period is defined as the day from first dose of study drug to the last dose of study drug.
- The post-treatment period is defined as the time after the last dose of study drug.

Treatment-emergent AEs (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Analysis

- Incidence and severity of ocular and non-ocular adverse events (AEs) and serious AEs

8. 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 Cleveland Clinic.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (e.g., AEs, applicable baseline findings, medication, medical history / surgical history/ophthalmic history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with a paper Data Capture tool.

8.1 Electronic Systems

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

- Epic– EMR system
- Statistical Analysis Software (SAS) – statistical review and analysis
- REDCap database system – CRF collection

9. STUDY MONITORING

9.1 Monitoring of Study Sites

The study coordinator will review all documentation prior to enrollment of the first subject, and periodically during the study. In accordance with International Conference on Harmonization (ICH) guidelines, the coordinator will compare the eCRF entries with the appropriate source documents. Additional review may include, but is not limited to, subject ICFs, documentation of subject recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the designee upon request.

9.2 Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate subject records (source documents).

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

9.3 Case Report Form Requirements

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

10. AUDITS AND INSPECTIONS

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

- Informing the designee of a planned inspection by the authorities as soon as notification is received, and authorizing the designee's participation in the inspection

- 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 designee immediately
- Taking all appropriate measures requested by the designee 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 addition, representatives of the designee may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

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

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Good Clinical Practice Statement

It is the responsibility of both the designee and 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 subject prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the subject in language that he/she can understand. The ICF should be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

- Subjects who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Subjects who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

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

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study subjects must be informed of

the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the subject's study record and a copy must be given to the subject.

11.3 Subject Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. Subjects should be identified by their initials and a subject identification number, only, on CRFs or other documents submitted to the designee. Documents that will not be submitted to the designee (e.g., signed ICF) must be kept in strict confidence.

The subject's and investigators personal data, which may be included in the investigator's study database, will be treated in compliance with all applicable laws and regulations. The investigator shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

11.4 Institutional Review Board

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

- The protocol, ICF, and any other materials to be provided to the subjects (e.g., advertising) before any subject may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the IRB should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

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

A copy of the IRB approval letter with a current list of the IRB members and their functions must be received by Regeneron prior to shipment of drug supplies to the investigator. The approval letter should 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) must be kept on file by the investigator.

12. PROTOCOL AMENDMENTS

The investigator may 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

Cleveland Clinic or Regeneron has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others.

14. STUDY DOCUMENTATION

14.1 Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the designee with the final set of CRFs for each subject.

14.2 Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 2 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the designee before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the designee and the relevant records will be transferred to a mutually agreed-upon destination.

15. 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 IAI.

- Preparation (please see below regarding the optional use of topical antibiotic agents pre and post dose):
    a. Apply topical anesthetic with or without subconjunctival 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 povidone-iodine on the ocular surface at the intended injection site.
    d. A sterile speculum may be used.
    e. Mark the injection site location with an empty Tb syringe.
    f. Apply additional drop of povidone-iodine to site of injection.

- Study Drug (VEGF Trap-Eye) Administration:
    a. Insert needle at marked injection point.
    b. Gently inject study drug.
    c. As the needle is withdrawn, a sterile cotton tip applicator may be rolled over the entry site to minimize the risk of drug reflux.

- Post-Injection Procedures

  Confirm that the patient has at least counting fingers vision. See guidelines below for additional post-injection management procedures.

Guidelines for Pre and Post-injection Management

- Use of Topical Antibiotic Agents

  No pre or post-injection antibiotics will be used.

- If vision is less than Counting Fingers:

  Visualize the optic nerve to verify reperfusion of the central retinal artery in the immediate post-injection period.

  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 or the patient remains less than count fingers for more than 1 to 2 minutes with an IOP > 35 mm Hg.

- 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.

16. Appendix 2: Critical References

1. Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. Endocr Rev. 1997 Feb;18(1):4-25.

2. Ferrara N, Houck KA, Jakeman LB, Winer J, Leung DW. The vascular endothelial growth factor family of polypeptides. J Cell Biochem. 1991 Nov;47(3):211-8.

3. Ferrara N. Vascular endothelial growth factor and the regulation of angiogenesis. Recent Prog Horm Res. 2000;55:15-35; discussion 35-6.

4. Rakic JM, Lambert V, Devy L, Luttun A, Carmeliet P, Claes C, Nguyen L, Foidart JM, Noël A, Munaut C. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. Invest Ophthalmol Vis Sci. 2003 Jul;44(7):3186-93.

5. Thickett DR, Armstrong L, Millar AB. Vascular endothelial growth factor (VEGF) in inflammatory and malignant pleural effusions. Thorax. 1999 Aug;54(8):707-10.

6. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. Br J Ophthalmol. 2012 May;96(5):694-8