Clinical Study Protocol

Intravitreal Aflibercept for Retinal Non-Perfusion in Proliferative Diabetic Retinopathy (The RECOVERY Study)

Compound:	Intravitreal Aflibercept Injection
Study Name:	RECOVERY
Clinical Phase:	II
Date of Issue:	October 19, 2017

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE	Intravitreal Aflibercept for Retinal Non-Perfusion in Proliferative Diabetic Retinopathy (The RECOVERY Study)
SITE LOCATION(S)	Retina Consultants of Houston, Houston, Texas 6560 Fannin, Ste 750 Houston, TX 77030 Retina Consultants of Houston, The Woodlands, Texas 17350 St. Luke's Way, Ste 120 The Woodlands, TX 77384 Retina Consultants of Houston, Kingwood 350 Kingwood Medical Drive, Ste 200 Kingwood, TX 77339 Retina Consultants of Houston, Katy 23501 Cinco Ranch Blvd, Ste G205 Kingwood, TX 77494
Principal Investigator	Charles C. Wykoff, MD, PhD

OBJECTIVE(S)	Primary Objectives • Assess the safety and tolerability of IAI for the treatment of proliferative diabetic retinopathy by evaluating the incidence and severity of ocular and systemic adverse events through week 100 • Change in area of retinal capillary non-perfusion, as assessed by central reading center, from baseline through week 100 Secondary Objectives • Assess the safety and tolerability of IAI for the treatment of proliferative diabetic retinopathy by evaluating the incidence and severity of ocular and systemic adverse events baseline through week 52 and baseline through week 100 • Change in area of retinal capillary non-perfusion, as assessed by central reading center, from baseline through week 52 and baseline through week 100 • Mean change in Early Treatment of Diabetic Retinopathy Severity Best Corrected Visual Acuity (ETDRS-BCVA) from baseline through week 52 and baseline through week 100 • Change in area of retinal capillary non-perfusion within the macula, as assessed by ultrawide-field fluorescein from baseline through week 52 and baseline through week 100 • Change in area of retinal capillary non-perfusion outside of the macula from baseline through week 52 and baseline through week 100 • Percentage of subjects with neovascularization regression from baseline through week 52 and baseline through week 100 • Percentage of subjects with increased neovascularlization from baseline through week 52 and baseline through week 100 • Percentage of subjects who develop vitreous hemorrhage from baseline through week 52 and baseline through week 100 • Percentage of subjects treated with PRP or vitrectomy for progression of PDR from baseline through week 52 and baseline through week 100 • Percentage of subjects, at week 52 and week 100, who develop center-involving diabetic macular edema who did not have center-involving diabetic macular edema at baseline • Changes in visual function outcomes (Humphrey visual field and self-reported visual function) from baseline through week 52 and baseline through week 100 • Mean change in central retinal thickness (CRT) from baseline through week 52 and baseline through week 100
STUDY DESIGN	Open Label
STUDY DURATION	100 weeks
ESTIMATED STUDY COMPLETION DATE	June 2019
POPULATION	
Sample Size:	40
Target Population:	Men or women 18 years and older with retinal non-perfusion (RNP) associated with proliferative diabetic retinopathy (PDR).
TREATMENT(S)	
Study Drug:	Aflibercept
Dose/Route/	Study eyes will be assigned randomly (1:1 ratio) to one of the following 2 treatment arms:

Schedule:

- **Group 1**- aflibercept 2 mg every 4 weeks (defined as every 28 days (± 7 days) and at least 21 days between injections) through week 48. Subjects will have a mandatory Year 1 visit at week 48. Subjects have a mandatory visit at week 52 and will not receive treatment. During the second year of follow-up, subjects will be monitored and treated every 12 weeks (Week 60, 72, 84 and 96) with an end of study visit at week 100. If NV or PDR are worse per the pre-specified criteria at week 60, or at any study visit thereafter, the subject will be treated monthly through the end of the study.

- **Group 2** - aflibercept 2 mg every 12-weeks for 48 weeks. Subjects will be followed every 4 weeks through week 12, and can be treated if the pre-specified criteria are met. Starting at week 12 if NV or PDR are stable or improved (as assessed by investigator) the subject will be monitored and treated at a 12-week interval through week 48. If NV or PDR are worse per the pre-specified criteria at week 12, or at any study visit thereafter, the subject will be treated monthly through week 48. At week 52 –
  - For subjects without any retinal non-perfusion, monitoring and treatment will continue at every 12 weeks (Week 60, 72, 84, 96) with an end of study visit at week 100.
  - For subjects with visible retinal non-perfusion, monitoring and treatment will be at a 4-week interval (defined as every 28 days + 7 days and at least 21 days between injections). If retinal non-perfusion has completely resolved at week 72, the subject will be switched back to monitoring and treatment every 12 weeks (Week 72, 84, 96).

Pre-specified criteria (subject must meet at least one criterion which must be documented with imaging):

- Increased neovascularization
- Decrease in BCVA by 5 or more letters due to progressive DME or PDR
- Worsening central subfield diabetic macular edema causing vision loss, with principal investigator or other delegated investigator confirmation
- Total area of retinal ischemia increases by 10% as determined by the central reading center

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1.1 Introduction

Diabetic retinopathy (DR) is a leading cause of visual loss around the world, and remains the most common cause of blindness among working age people in the United States (USA) and many developed countries[1]. Through pathologic retinal ischemia DR leads to visual loss primarily through diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).

PDR is defined by the development of neovascularization (NV) that originates from the retinal vasculature and aberrantly grows through the internal limiting membrane into the vitreous. Retinal NV can either involve the optic disc (NVD) or more peripheral retina (NVE). PDR typically leads to visual loss through either rupture of the unstable, pathologic vessels causing vitreous hemorrhage (VH) or retinal distortion and traction-detachments due to concurrent proliferation of a fibrous scaffold along with the abnormal vessels.

Epidemiologic data suggests that given a long enough duration of diabetes, approximately 60% of diabetics will develop PDR[2]. Such transition to PDR significantly increases the risk of progressive visual loss and without intervention, approximately half of eyes will ultimately experience severe visual loss[3]. Currently, PDR results in 12,000 to 24,000 new cases of blindness each year in the USA[4].

Validated through the Diabetic Retinopathy Study, panretinal photocoagulation (PRP) has been the standard treatment for PDR since the 1970s[5]. Application of appropriate PRP reduces the risk of severe visual loss to approximately 4%[6]. However, despite its effectiveness for PDR treatment, PRP can have substantial untoward effects including peripheral visual field defects, night vision loss, loss of contrast sensitivity, and loss of visual acuity (VA); furthermore, PRP itself can be incompletely effective in some eyes, with subsequent need for additional PRP in nearly half of patients[4] and need for traditional vitrectomy surgical intervention in at least 5% of eyes despite appropriate laser treatment[7].

Therefore, supplemental or alternative therapies for PDR could be of substantial clinical value. Pathologic over-expression of vascular endothelial growth factor-A (VEGF)[8] is a key driver of DR, DME and PDR. Pharmaceutical agents that specifically inhibit VEGF including aflibercept (Eylea, Regeneron), ranibizumab (Lucentis, Genentech), and bevacizumab (Avastin, Genentech) have revolutionized the management of DME. These medications are remarkably well-tolerated by patients and administered in the clinic using a 30-gauge or smaller needle inserted through the pars plana directly into the vitreous cavity.

Multiple prospective, randomized trials focusing on the management of DME have demonstrated that anti-VEGF therapy can significantly blunt the progression of DR to PDR. For example, PDR events were reduced in the RIDE/RISE phase 3 trials at 2 years from approximately 34% with sham treatment to 11% with monthly ranibizumab treatment (either 0.3mg or 0.5mg)[9, 10]. Anti-VEGF treatments have the additional benefit of not only slowing progression to PDR but also improving diabetic retinopathy severity scales (DRSS) in a substantial proportion[10, 11], a clinical finding not observed with PRP alone. For example, in the RISE/RIDE trials at 2-years, 35.9-37.2% of ranibizumab treated eyes experienced ≥2 step DRSS improvements compared to 5.4% of sham treated eyes[9]. Similarly, at the 2-year point

of VISTA/VIVID study program, 29.3-37.1% of aflibercept treated eyes experienced ≥2 step DRSS improvements compared to 8.2-15.6% of sham-treated eye[11].

The Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol S, *Prompt PRP versus Intravitreous Ranibizumab with Deferred PRP for PDR,* stands as the first large, prospective trial to directly compare PRP to anti-VEGF treatment specifically for the management of PDR[4].

This trial randomized 394 eyes with PDR at 55 sites across the USA to either baseline PRP or intravitreal ranibizumab (0.5mg) injections[4]. At the 2-year primary endpoint, non-inferiority of ranibizumab compared to PRP was achieved with a mean VA improvement of +2.8 vs +0.2 letter in the ranibizumab and PRP arms respectively. While VA outcomes were similar between the arms, secondary efficacy outcomes strongly favored the anti-VEGF treatment arm. Mean Humphrey visual field sensitivity loss was worse, vitrectomy was more frequent, and DME development was more common in the PRP vs anti-VEGF groups, findings that were all highly statistically significant (P<0.001).

The role of anti-VEGF pharmaceuticals in the management of advanced forms of DR may be much more important than blunting progression to PDR and obviating the negative consequences of PRP. Indeed, the mechanism by which VEGF blockade leads to DRSS improvements may be fundamental to the underlying disease process of DR itself: retinal vascular perfusion. Specifically, VEGF blockade in the context of DR appears to have a significant impact on the underlying retinal vasculature. In RISE/RIDE, development of angiographically-identified RNP was significantly reduced at 2 years from approximately 30% to <10% with monthly VEGF blockade[12]. Ongoing prospective angiographic analyses of patients with moderately severe and severe NPDR, corresponding to DRSS levels 47 and 53, in the randomized DRCR-W and PANORAMA studies may provide further evidence of anti-VEGF-medicated modification of RNP using aflibercept.

Preliminary data from a small series involving eyes with PDR presented by Jeff Heier, MD in October, 2015 indicate that some eyes may experience substantial and impressive RNP improvements with aflibercept treatment[13]. More data is needed to further understand the effect of aflibercept treatment on RNP in PDR.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of 2 mg intravitreal aflibercept injections (IAI) given monthly (Q4WK) or every 12 weeks (Q12WK) for the treatment of retinal capillary non-perfusion (RNP) associated with proliferative diabetic retinopathy (PDR).

- Assess the safety and tolerability of IAI for the treatment of proliferative diabetic retinopathy by evaluating the incidence and severity of ocular and systemic adverse events through week 52
- Change in area of retinal capillary non-perfusion, as assessed by central reading center, from baseline through week 52

2.2 Secondary Objective(s)

The secondary objectives of the study are:

- Assess the safety and tolerability of IAI for the treatment of proliferative diabetic retinopathy by evaluating the incidence and severity of ocular and systemic adverse events through week 100
- Change in area of retinal capillary non-perfusion, as assessed by central reading center, from baseline through week 100
- Mean change in Early Treatment of Diabetic Retinopathy Severity Best Spectacle Corrected Visual Acuity (ETDRS-BCVA) from baseline through week 52 and baseline through week 100
- Change in area of retinal capillary non-perfusion within the macula, as assessed by ultrawide-field fluorescein from baseline through week 52 and baseline through week 100
- Change in area of retinal capillary non-perfusion outside of the macula from baseline through week 52 and baseline through week 100
- Percentage of subjects with neovascularization regression from baseline through week 52 and baseline through week 100
- Percentage of subjects with increased neovascularlization from baseline through week 52 and baseline through week 100
- Percentage of subjects who develop vitreous hemorrhage from baseline through week 52 and baseline through week 100
- Percentage of subjects treated with PRP or vitrectomy for progression of PDR, from baseline through week 52 and baseline through week 100
- Percentage of subjects at week 52 and week 100, who develop center-involving diabetic macular edema who did not have center-involving diabetic macular edema at baseline
- Changes in visual function outcomes (Humphrey visual field and self -reported visual function) from baseline through week 52 and baseline through week 100
- Mean change in central retinal thickness (CRT) from baseline through week 52 and baseline through week 100

3. STUDY DESIGN

3.1 Study Description and Duration

RECOVERY will assess the safety and tolerability of 2 mg intravitreal aflibercept injections (IAI) given monthly (Q4WK) or every 12 weeks (Q12WK) for the treatment of retinal non-perfusion (RNP) associated with proliferative diabetic retinopathy (PDR) primarily assessed through retinal capillary non-perfusion.

3.2 Rational for Study Extension

Diabetes and diabetic retinopathy are chronic, typically progressive diseases. Longer term follow-up beyond a single year of treatment potentially informing clinical management is valuable. Monthly dosing indefinitely is a huge challenge and a clear barrier to optimal care delivery. If monthly IAI improves vascular perfusion in the population as a whole over the course of Year 1 of RECOVERY, as anticipated based on prior analyses such as the investigator initiated trial ANDROID, it will be valuable to determine if transition to dosing every 12 weeks can maintain the vascular benefits observed after the first year. For patients managed with every 12 week IAI dosing during Year 1 of RECOVERY, it will be valuable to determine if increased IAI dosing frequency to every month can result in additional vascular benefit.

3.3 Planned Interim Analysis

No interim analysis is planned.

3.4 Safety Plan

The safety and tolerability of IAI have been investigated in previous Phase I, I/II and III studies in AMD, RVO, and DME trials. Potential safety issues associated with the route of administration or the pharmacology of aflibercept in the study population include decreased BCVA, intraocular inflammation, intraocular infection, transient and/or sustained elevation of intraocular pressure (IOP), cataract development or progression, retinal or intraretinal hemorrhage, macular edema, retinal break or detachment, and arterial thromboembolic events (ATEs). Safety will be assessed by visual acuity, ophthalmic examinations, fluorescein angiograms, SD-OCT, intraocular pressure, vital signs, and adverse event documentation.

To minimize the risks of intraocular infections, all injections will be performed employing sterile techniques. Study drug administration will be held for subjects who experience certain ocular events or infections. In the event, any subject develops an adverse event in the study eye that is considered by the evaluating physician to be severe in intensity, serious consideration should be given to withdrawing the subject from the study.

The PI or designated Sub-Investigators will review all adverse events on an ongoing basis to determine causality and relationship to study drug and/or study procedures.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

4.1 Number of Subjects Planned

Approximately 40 subjects will be randomized into one of two treatment arms in a 1:1 ratio.

4.2 Study Population

The targeted study population is men or women 18 years and older with retinal non-perfusion (RNP) associated with proliferative diabetic retinopathy (PDR).

4.3 Inclusion Criteria

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

1. Men or women $\geq$ 18 years of age with type 1 or type 2 diabetes mellitus

2. BCVA ETDRS $\geq$ 20/400 in the study eye
3. Willing and able to comply with clinic visits and study-related procedures
4. Provide signed informed consent
5. Substantial non-perfusion (defined as greater than 20 disc areas), as assessed by the investigator
6. Early PDR, as assessed by the investigator, with no vitreous hemorrhage*

   * Early PDR is defined in which PRP can safely be deferred and vitreous hemorrhage that does not obscure the application of PRP

4.4 Exclusion Criteria

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

1. Any prior systemic anti-VEGF or IVT anti-VEGF treatment in the study eye,
2. SD-OCT central subfield thickness measurement of > 320 μm, in the study eye
3. Evidence of infectious ocular infection, in the study eye, at time of screening
4. History of vitreoretinal surgery in the study eye
5. Any prior Panretinal laser photocoagulation (PRP) in the study eye
6. Current vitreous hemorrhage obscuring retinal imaging in the study eye
7. Cataract surgery in the study eye within 4 weeks of Day 0
8. Uncontrolled blood pressure (defined as $\geq$ 180/110 mm Hg systolic/diastolic, while seated)
9. Significant renal disease defined as a history of chronic renal failure requiring dialysis or renal transplant
10. Tractional Retinal Detachment threatening the macula in the study eye
11. Corticosteroid treatment (intravitreal or peribulbar) in the study eye within 12 weeks of screening
12. Pregnant or breast-feeding women
13. Sexually active men* or women of childbearing potential who are unwilling to practice adequate contraception during the study. Adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device (IUD); bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly.

    *Contraception is not required for men with documented vasectomy.

4.5 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 and sponsor have 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 subjects 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.

4.6 Replacement of Subjects

Subjects prematurely discontinued from the study may be replaced at principal investigators discretion, if subject is discontinued before week 24.

5. STUDY TREATMENTS

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

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

Study eyes will be assigned randomly (1:1 ratio) to one of the following 2 treatment arms:

- **Group 1-** aflibercept 2 mg every 4 weeks (defined as every 28 days (+ 7 days) and at least 21 days between injections) through week 48. Subjects will have a mandatory Year 1 visit at week 48. Subjects have a mandatory visit at week 52 and will not receive treatment. During the second year of follow-up, subjects will be monitored and treated every 12 weeks (Week 60, 72, 84 and 96) with an end of study visit at week 100. If NV or PDR are worse per the pre-specified criteria at week 60, or at any study visit thereafter, the subject will be treated monthly through the end of the study.

- **Group 2** - aflibercept 2 mg every 12-weeks for 48 weeks. Subjects will be followed every 4 weeks through week 12, and can be treated if the pre-specified criteria are met. Starting at week 12 if NV or PDR are stable or improved (as assessed by investigator) the subject will be monitored and treated at a 12-week interval through week 48. If NV or PDR are worse per the pre-specified criteria at week 12, or at any study visit thereafter, the subject will be treated monthly through week 48. At week 52 –
    - For subjects without any retinal non-perfusion, monitoring and treatment will continue at every 12 weeks (Week 60, 72, 84, 96) with an end of study visit at week 100.
    - For subjects with visible retinal non-perfusion, monitoring and treatment will be at a 4-week interval (defined as every 28 days + 7 days and at least 21 days between injections). If retinal non-perfusion has completely resolved at week 72, the subject will be switched back to monitoring and treatment every 12 weeks (Week 72, 84, 96).

Pre-specified criteria (subject must meet at least one criterion, which must be documented with imaging):

1) Increased neovascularization

2) Decrease in BCVA by 5 or more letters due to progressive DME or PDR
3) Worsening central subfield diabetic macular edema causing vision loss, with principal investigator or other delegated investigator confirmation
4) Total area of retinal ischemia increases by 10% as determined by the central reading center or Princiapl Investigator

5.1 Rescue Treatment

At any point throughout the study, for either treatment arm, if PDR progresses despite 3 monthly IAI, a fluorescein angiogram will be performed to evaluate PDR progression. PRP will only be permitted after confirmation of PDR progression with the primary investigator.

5.2 Treatment Logistics and Accountability

5.2.1 Packaging, Labeling, and Storage

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

5.2.2 Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2° to 8°C to the investigator or designee at regular intervals or as needed during the study. At the end of the study and following drug reconciliation and documentation, all opened and unopened vials of study drug will be destroyed or returned to Regeneron Pharmaceuticals, Inc. or designee.

5.2.3 Treatment Accountability

All drug accountability records will be kept current.

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

- dispensed to each patient – or -

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

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

5.2.4 Treatment Compliance

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

5.3 Concomitant and Excluded Therapies

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

5.3.1 Study Eye

During the 100-week study period, only the treatments mandated by the study will be permitted for the study eye. The subject can have only one study eye in the study. If both eyes meet eligibility criteria at screening, the examining investigator will select the study eye.

5.3.2 Fellow Eye

The fellow eye may receive standard of care therapies necessary for the treatment of PDR or center-involving diabetic macular edema. If the fellow eye requires anti-VEGF treatments, Regeneron will provide IAI for FDA approved indications.

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

6.1 Schedule of Events

Study assessments and procedures are presented by study period and visit see table below.

Schedule of Events

	Screen/ Baseline	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days)	Week 16 (±7 days)	Week 20 (±7 days)	Week 24 (±7 days)	Week 28 (±7 days)	Week 32 (±7 days)	Week 36 (±7 days)	Week 40 (±7 days)	Week 44 (±7 days)	Week 48 (±7 days)	Week 52 (±7 days)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Informed Consent	X													
Demographics	X													
NEI VFQ 25	X												X	
Medical & Ophthalmic History	X													
Inclusion/ Exclusion	X													
Randomization	X													
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height & Weight	X													
Humphrey Visual Field (study eye)	X												X	
HbA1C	X												X	
Urine Pregnancy Test[6]	X													
Review of Concomitant Medications[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA (ETDRS)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy (study eye)	X												X	
Intraocular Pressure[2, 3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT-A[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optos FA & FP[3, 4]	X						X						X	
Indirect Ophthalmoscopy/Slit Lamp Examination[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer IVT aflibercept[7]	X	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X	X[3, 8]

1. Subjects who are withdrawn/discontinued from the study before week 100 will be asked to return to complete the week 100 assessments 30 days after their last study treatment
2. Intraocular pressure will be measured pre-dose (bilateral) using either Goldmann applanation or Tono-pen™ (the same method must be used on all subjects for study duration)
3. May be required for subjects who meet pre-specified criteria or subjects who require treatment at a 4-week interval
4. FP & FA must be performed on Optos before PRP is administered
5. Performed at sites who have access to required testing equipment at every visit and every 6 months for sites who do not have direct access
6. Only for women of childbearing potential, required prior to randomization
7. All procedures will be completed before administration of study treatment
8. Subjects in Group 1 will not receive treatment

	Week 56 (±7 days)	Week 60 (±7 days)	Week 64 (±7 days)	Week 68 (±7 days)	Week 72 (±7 days)	Week 76 (±7 days)	Week 80 (±7 days)	Week 84 (±7 days)	Week 88 (±7 days)	Week 92 (±7 days)	Week 96 (±7 days)	Week[1] 100 (±7 days)
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
Informed Consent												
Demographics												
NEI VFQ 25											X	
Medical & Ophthalmic History												
Inclusion/ Exclusion												
Randomization												
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X
Height & Weight												
Humphrey Visual Field (study eye)											X	
HbA1C											X	
Urine Pregnancy Test[6]												
Review of Concomitant Medications[3]	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events[3]	X	X	X	X	X	X	X	X	X	X	X	X
BCVA (ETDRS)[3]	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy (study eye)											X	
Intraocular Pressure[2, 3]	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT[3]	X	X	X	X	X	X	X	X	X	X	X	X
OCT-A[5]	X	X	X	X	X	X	X	X	X	X	X	X
Optos FA & FP[3, 4]					X						X	X[8]
Indirect Ophthalmoscopy/Slit Lamp Examination[3]	X	X	X	X	X	X	X	X	X	X	X	X
Administer IVT aflibercept[7]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X	

1, Subjects who are withdrawn/discontinued from the study before week 100 will be asked to return to complete the week 100 assessments 30 days after their last study treatment
2. Intraocular pressure will be measured pre-dose (bilateral) using either Goldmann applanation or Tono-pen™ (the same method must be used on all subjects for study duration)
3. May be required for subjects who meet pre-specified criteria or subjects who require treatment at a 4-week interval
4. FP & FA must be performed on Optos before PRP is administered
5. Performed at sites who have access to required testing equipment at every visit and every 6 months for sites who do not have direct access
6. Only for women of childbearing potential, required prior to randomization
7. All procedures will be completed before administration of study treatment
8. FP only will be performed at week 100

6.2 Study Visit Descriptions

All procedures will be performed before injection and bilaterally unless otherwise indicated.

Screening/Baseline

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

- Inclusion/exclusion
- Demographics (race, ethnicity, etc)
- Height & Weight
- Review of medical history and concurrent illnesses
- Review of concomitant medications
- Review of adverse events

The following procedures and assessments will be conducted:

- NEI VFQ25
- Vital signs
- Urine pregnancy test (if applicable)
- Humphrey Visual Field (Study Eye)
- IOP (pre-dose bilateral)
- BCVA ETDRS
- Gonioscopy (Study Eye)
- SD-OCT
- OCT Angiography
- Optos Fundus Photos
- Optos Fluorescein Angiography
- Hemoglobin A1C
- Indirect Ophthalmoscopy
- Slit Lamp
- IAI (Study Eye)

Weeks 4, 8, 16, 20, 28, 32, 40, 44 (Group 1)

The following information will be collected:

- Review of concomitant medications
- Review of adverse events

The following procedures and assessments will be conducted:

- Vital signs
- IOP (pre-dose bilateral)
- BCVA (ETDRS)
- SD-OCT
- OCT Angiography
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye)**

** If subjects are being monitored Q12WKS and require visits on a more frequent basis, the above listed procedures and assessments will be performed at those visits, but may or may not require IAI in the study eye. Q12WKS arm can be seen for more frequent visits every Q4WKS (28 +/- 7 days).

Weeks 4 & 8 (Group 2)

The following information will be collected:

- Review of concomitant medications
- Review of adverse events

The following procedures and assessments will be conducted:

- Vital signs
- IOP (pre-dose bilateral)
- BCVA (ETDRS)
- SD-OCT
- OCT Angiography
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye) **

**Can be treated with IAI if NV or PDR are worse (as assessed by investigator).

Weeks 12, 36 (Group 1 & 2)

The following information will be collected:

- Review of concomitant medications
- Review of adverse events

The following procedures and assessments will be conducted:

- Vital signs
- IOP (pre-dose bilateral)
- BCVA (ETDRS)
- SD-OCT
- OCT Angiography
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye)

Week 24 (Group 1 & 2)

The following information will be collected:

- Review of concomitant medications
- Review of adverse events

The following procedures and assessments will be conducted:

- Vital signs
- IOP (pre-dose bilateral)
- BCVA (ETDRS)
- SD-OCT
- OCT Angiography
- Optos Fundus Photos
- Optos Fluorescein Angiography
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye)

Week 48 (Groups 1 & 2)

The following information will be collected:

- Review of concomitant medications
- Review of adverse events

The following procedures and assessments will be conducted:

- NEI VFQ25

- Vital signs
- Humphrey Visual Field (Study Eye)
- IOP (pre-dose bilateral)
- ETDRS BCVA
- Gonioscopy (Study Eye)
- SD-OCT
- OCT Angiography
- Optos Fundus Photos
- Optos Fluorescein Angiography
- Hemoglobin A1C
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye- Group 2) (Group 1 will not be treated)

Week 52 (Mandatory Visit- Group 1 & 2)

The following information will be collected:

- Review of concomitant medications
- Review of adverse events

The following procedures and assessments will be conducted:

- Vital signs
- IOP (pre-dose bilateral)
- ETDRS BCVA
- SD-OCT
- OCT Angiography
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye)

Week 56, 60, 64, 68, 76, 80, 84, 88, 92 (Group 1 & Group 2 subjects that will remain on a 12-week treatment interval) (Group 2-subjects on every 4-week treatment interval)

The following information will be collected:

- Review of concomitant medications

- Review of adverse events

The following procedures and assessments will be conducted:

- Vital signs
- IOP (pre-dose bilateral)
- ETDRS BCVA
- SD-OCT
- OCT Angiography
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye)

** If subjects are being monitored Q12WKS and require visits on a more frequent basis, the above listed procedures and assessments will be performed at those visits, but may or may not require IAI in the study eye. Q12WKS arm can be seen for more frequent visits every Q4WKS (28 +/- 7 days).

Week 72 (Group 1 & 2)

The following information will be collected:

- Review of concomitant medications
- Review of adverse events

The following procedures and assessments will be conducted:

- Vital signs
- IOP (pre-dose bilateral)
- ETDRS BCVA
- SD-OCT
- OCT Angiography
- Optos Fundus Photos
- Optos Fluorescein Angiography
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye)

Week 96 (Group 1 & 2)

The following information will be collected:

- Review of concomitant medications
- Review of adverse events

The following procedures and assessments will be conducted:

- NEI VFQ25
- Vital signs
- IOP (pre-dose bilateral)
- ETDRS BCVA
- Humphrey Visual Field (Study Eye)
- Gonioscopy (Study Eye)
- SD-OCT
- OCT Angiography
- Optos Fundus Photos
- Optos Fluorescein Angiography
- Hemoglobin A1C
- Indirect Ophthalmoscopy
- Slit Lamp Exam
- IAI (Study Eye)

Week 100 (Groups 1 & 2)

The following information will be collected:

- Review of concomitant medications
- Review of adverse events

The following procedures and assessments will be conducted:

- Vital signs
- IOP (pre-dose bilateral)
- ETDRS BCVA
- SD-OCT
- OCT Angiography
- Optos Fundus Photos
- Indirect Ophthalmoscopy

- Slit Lamp Exam

6.2.1 Early Termination Visit

Subjects who withdraw from the study prior to completion should return for an early termination evaluation 28 days (± 7 days) following the last injection/study visit for monitoring of all adverse events (serious and non-serious). The schedule of assessments for early termination is the same as that for week 100 described in section 6.1.

6.3 Study Procedures

*Refer to section 6.1 for a schedule of study procedures

Safety Procedures

Best Corrected Visual Acuity

Visual function of the study eye and fellow eye will be assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985) at 4 meters at every visit.

Intraocular Pressure

Intraocular pressure (IOP) of both eyes will be measured pre-dose at every visit. The method used for IOP measurement for a subject must remain consistent throughout the study.

Gonioscopy

Subjects will be evaluated for the development of neovascularization of the iridocorneal angle by gonioscopy in conjunction with slit lamp examination.

Slit Lamp Examination

Subject's anterior eye structure and ocular adnexa of both eyes will be examined at every visit using a slit lamp, pre-dose, by the PI or Sub-Investigator.

Indirect Ophthalmoscopy

Subject's posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at every visit, pre-dose by the PI or Sub-Investigator.

Optical Coherence Tomography (SD-OCT)

Ocular morphology will be evaluated at every visit using the Heidelberg Spectralis SD-OCT. Starting with screening visit images will be captured for both eyes. All SD-OCTs will be electronically archived at the site as part of the source documentation.

Fundus Photography/Fluorescein Angiography

The anatomical state of the retinal vasculature will be evaluated using Optos Fundus Photography (FP) and Optos Fluorescein Angiography (FA). The machine used to perform FA on a subject must remain consistent throughout study. FP and FA will be captured for both eyes. All FPs and FAs will be archived at the site as a part of source documentation.

Vital Signs

Vital signs will include measurements of pulse, systolic and diastolic blood pressure while the subject is in a seated position. Vital signs should be taken pre-dose at every visit.

Visual Field Testing

Visual field testing will be assessed in the study eye using the Humphrey visual 30-2 according to section 6.1.

Laboratory Testing

HbA1C will be collected at screening, week 52, and week 100 or early term visits prior to study drug injection (if applicable). If a subject has had an HbA1C collected within 60 days of screen those results can be used and does not need to be repeated at screen, as long as site is able to receive proper documentation prior to randomization.

If subjects are of childbearing potential a urine dipstick will be collected at the screening visit prior to study drug injection.

6.3.1 Adverse Event Information Collection

The investigator (or designee) will record all AEs that occur during the study starting with the time the informed consent is signed through end of study on AE logs.

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

6.3.2 Adverse Events of Special Interest

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the investigational product.

The aflibercept Events of Special Interest are:

- Retinal pigment epithelial tear
- Increased intraocular pressure > 30 mmHg not responsive to maximal topical IOP-lowering drugs measured on two separate days
- Traumatic cataract
- Endophthalmitis
- Intraocular inflammation of > 2+ cell (including vitritis and uveitis)
- Retinal detachment
- ATEs, including stroke

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 one 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.

7.1.3 Criteria for Serious Sight-Threatening Ocular Adverse Events

Criteria for serious sight-threatening ocular AEs include the following:

- Adverse event causes a decrease in BCVA of > 30 letters (compared with the most recent assessment of BCVA)

- Adverse event causes a decrease in VA to the level of light perception or worse

- Adverse event requires surgical intervention (eg, vitreous tap or biopsy with IVT injection of anti-invectives, laser or retinal cryopexy with gas) to prevent permanent loss of sight

- In the opinion of the investigator, AE may require medical intervention to prevent permanent loss of sight

Criteria for reporting SAEs must be followed for these events. Drug may be held if any sight-threatening ocular adverse event occurs, at discretion of treating investigator.

7.2 Recording and Reporting Adverse Events

All AEs and SAEs will be recorded in the patient's source documents using medical terminology. Laboratory values or vital signs will be recorded as AEs only if they are medically relevant in the opinion of the investigator.

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

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

7.2.1 Deaths

Any AE that results in death is considered 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

7.2.2 Pregnancy and Other Events that Require Accelerated Reporting

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

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

Pregnancy: Although it is not considered an AE, the investigator will report to Regeneron Pharmaceuticals, Inc., any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 30 days following the last dose of study drug. The investigator will follow the pregnancy until delivery, or longer. If the pregnancy continues to term (delivery), the health of the infant will also be reported to Regeneron Pharmaceuticals, Inc.

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

Medical.safety@regeneron.com

Fax: 914-345-7476

SAE hotline: 914-593-1504

7.2.3 Reporting Adverse Events Leading to Withdrawal from the Study

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

Medical.safety@regeneron.com

Fax: 914-345-7476

SAE hotline: 914-593-1504

7.2.4 Abnormal Laboratory or Vital Signs

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

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

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

7.2.5 Follow-up

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

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

7.3 Evaluation of Severity and Causality

7.3.1 Evaluation of Severity

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

- **Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

7.3.2 Evaluation of Causality

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

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

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

8. STUDY VARIABLES

8.1 Demographic and Baseline Characteristics

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

8.2 Primary and Secondary Endpoints

The primary endpoint of this study is to assess the safety and tolerability of 2 mg intravitreal aflibercept injections (IAI) given monthly or every 12 weeks for the treatment of retinal capillary non-perfusion (RNP) associated with proliferative diabetic retinopathy (PDR).

- Assess the safety and tolerability of IAI for the treatment of proliferative diabetic retinopathy by evaluating the incidence and severity of ocular and systemic adverse events through week 52
- Change in area of retinal capillary non-perfusion, as assessed by central reading center, from baseline to week 52

Secondary Endpoints(s)

The secondary objectives of the study are:

- Assess the safety and tolerability of IAI for the treatment of proliferative diabetic retinopathy by evaluating the incidence and severity of ocular and systemic adverse events through baseline through week 52 and baseline through week 100
- Change in area of retinal capillary non-perfusion, as assessed by central reading center, from baseline through week 100
- Mean change in Early Treatment of Diabetic Retinopathy Severity Best Spectacle Corrected Visual Acuity (ETDRS-BCVA) from baseline through week 52 and baseline through week 100
- Change in area of retinal capillary non-perfusion within the macula, as assessed by ultrawide-field fluorescein from baseline through week 52 and baseline through week 100
- Change in area of retinal capillary non-perfusion outside of the macula from baseline through week 52 and baseline through week 100
- Percentage of subjects with neovascularization regression from baseline through week 52 and baseline through week 100
- Percentage of subjects with increased neovascularlization from baseline through week 52 and baseline through week 100

- Percentage of subjects who develop vitreous hemorrhage from baseline through week 52 and baseline through week 100
- Percentage of subjects treated with PRP or vitrectomy for progression of PDR from baseline through week 52 and baseline through week 100
- Percentage of subjects, at week 100, who develop center-involving diabetic macular edema who did not have center-involving diabetic macular edema at baseline
- Changes in visual function outcomes (Humphrey visual field and self-reported visual function), from baseline through week 52 and baseline through week 100
- Mean change in central retinal thickness (CRT) from baseline through week 52 and baseline through week 100

8.3 Analysis Sets

Efficacy Analysis Sets

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

Safety Analysis Set

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

8.4 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. Source documents must be available at all times for inspection by authorized representatives of regulatory authorities.

9. ETHICAL AND REGULATORY CONSIDERATIONS

9.1 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.

9.2 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, in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.
- 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.

9.3 Subject Confidentiality and Data Protection

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

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

9.4 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 (eg, 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 Pharamceuticals, Inc 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.

10. PROTOCOL AMENDMENTS

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

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

11.1 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 subject's interests.

12. STUDY DOCUMENTATION

12.1 Certification of Accuracy of Data

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

12.2 Retention of Records

The investigator will retain all essential study documents, including ICFs, source documents, CRFs, and drug accountability records for at least 3 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. Records will be destroyed in a manner that ensures confidentiality.

13. REFERENCES

1. Kempen JH, O'Colmain BJ, Leske MC, et al. The prevalence of diabetic retinopathy among adults in the United States. Archives of ophthalmology. 2004;122(4):552-563.

2. Klein R, Klein BE, Moss SE. A population-based study of diabetic retinopathy in insulin-using patients diagnosed before 30 years of age. Diabetes care. 1985;8 Suppl 1:71-76.

3. Preliminary report on effects of photocoagulation therapy. The Diabetic Retinopathy Study Research Group. American journal of ophthalmology. 1976;81(4):383-396.

4. Writing Committee for the Diabetic Retinopathy Clinical Research N, Gross JG, Glassman AR, et al. Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA : the journal of the American Medical Association. 2015;314(20):2137-2146.

5. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group. Ophthalmology. 1981;88(7):583-600.

6. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5 Suppl):766-785.

7. Ferris F. Early photocoagulation in patients with either type I or type II diabetes. Transactions of the American Ophthalmological Society. 1996;94:505-537.

8. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. The New England journal of medicine. 1994;331(22):1480-1487.

9. Ip MS, Domalpally A, Hopkins JJ, et al. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. Archives of ophthalmology. 2012;130(9):1145-1152.

10. Ip MS, Domalpally A, Sun JK, et al. Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. Ophthalmology. 2015;122(2):367-374.

11. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology. 2015;122(10):2044-2052.

12. Campochiaro PA, Wykoff CC, Singer M, et al. Monthly versus as-needed ranibizumab injections in patients with retinal vein occlusion: the SHORE study. Ophthalmology. 2014;121(12):2432-2442.

13. Heier J. The Effect of Intravitreal Aflibercept on Capillary Non-perfusion in Patients with Proliferative Retinopathy and/or Macular Edema Secondary to Proliferative Diabetic Retinopathy and Central Retinal Venous Occlusive Disease (ANDROID Study). Retina Society, Paris, France. 2015.