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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 3, DOUBLE-MASKED, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF INTRAVITREAL AFLIBERCEPT INJECTION IN PATIENTS WITH MODERATELY SEVERE TO SEVERE NONPROLIFERATIVE DIABETIC RETINOPATHY

Compound:	Intravitreal Aflibercept Injection
Clinical Phase:	3
Protocol Number:	VGFTe-OD-1411
Protocol Version:	VGFTe-OD-1411 Amendment 5
Amendment 5 Date of Issue:	*See appended electronic signature page*
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Scientific/Medical Monitor:	[redacted] Director, Clinical Sciences, Ophthalmology Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

Amendment 5

The purpose of this amendment is to change the time point for evaluation of the secondary endpoints from week 100 to week 52.

The secondary outcome measures include assessment of parameters associated with the prevention of vision threatening complications secondary to diabetic retinopathy, and central-involved diabetic macular edema (DME). These secondary outcome measures were to be analyzed in an exploratory manner at week 52 and formally tested at week 100. At week 24, these measures were assessed from a safety perspective, and there was a remarkable separation between the Intravitreal Aflibercept Injection (IAI) and sham groups. This separation was highly suggestive that IAI has a profound impact on these outcomes in diabetic retinopathy patients. In light of these results, Regeneron feels that it is important to make these data available to the diabetic retinopathy community through approved labeling as soon as possible.

Change	**Sections Changed**
Change the timepoint for evaluation of the secondary endpoints from week 100 to week 52, with additional exploratory analysis of the secondary endpoints at week 100.	Clinical Study Protocol Synopsis: Endpoints, Statistical Plan Figure 1 Study Flow Diagram Section 8.2 Primary and Secondary Variables Section 9.1 Statistical Hypothesis Table 4 Significance Levels for Testing Secondary Efficacy Endpoints Section 9.5.2 Efficacy Analyses Section 9.5.2.1 Analyses of Primary and Secondary Efficacy Variables

Amendment 3

The purpose of this amendment is to update exclusion criterion #16 to exclude women who are breastfeeding from participation in the study.

Change	**Sections Changed**
Exclusion updated: "16. *Women who are breastfeeding or who have a* positive serum hCG/urine pregnancy test at the screening or baseline visit".	Section 4.2.2 Exclusion Criteria (#16)
Added EudraCT Number.	Title Page

Amendment 2

The purpose of this amendment is to incorporate the following revisions in response to feedback from the Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA):

- Revise the significance levels for testing of the secondary efficacy endpoints, per FDA feedback
- Add a hemoglobin A1c (HbA1c) assessment at week 24, and fundus photography (FP) at week 8, per PMDA feedback

Amendment 1

The purpose of this amendment is to incorporate the following changes and clarifications following discussions with the FDA:

- The primary outcome measure of the study will be the proportion of patients who have improved by ≥2 steps from baseline in the Diabetic Retinopathy Severity Scale (DRSS) score at week 24 in the combined 2Q8 and 2Q16 groups, and at week 52 for each group separately.
- Secondary endpoints have been modified slightly; a few have been separated into 2 endpoints.
- The 2Q8 group will transition to a flexible dosing regimen based on the investigator's assessment of DRSS score beginning at week 56.

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3, Double-Masked, Randomized Study of the Efficacy and Safety of Intravitreal Aflibercept Injection in Patients with Moderately Severe to Severe Nonproliferative Diabetic Retinopathy
Site Locations	Approximately 70 sites.
Objectives	The primary objective of the study is to assess the efficacy of intravitreal (IVT) aflibercept compared to sham treatment in the improvement of moderately severe to severe nonproliferative diabetic retinopathy (NPDR). The secondary objectives of the study are: • To characterize the safety of IVT aflibercept in patients with moderately severe to severe NPDR • To determine if IVT aflibercept will prevent the worsening of diabetic retinopathy and reduce the incidence of diabetic macular edema (DME) • To determine the anatomic effects of IVT aflibercept in patients with moderately severe to severe NPDR.
Study Design	This is a phase 3, double-masked, randomized study of the efficacy and safety of IVT aflibercept for the improvement of moderately severe to severe NPDR. Eligible patients will be enrolled into 1 of 3 treatment groups in a 1:1:1 randomization scheme, and will be stratified based on their Diabetic Retinopathy Severity Scale (DRSS) score (level 47 vs. level 53). Only 1 eye will be selected as the study eye. The 3 treatment groups will have the following dosing regimens from day 1 to week 48: 1) every 8 weeks (2Q8) aflibercept IVT after 5 initial monthly doses; 2) every 16 weeks (2Q16) aflibercept IVT after 3 initial monthly doses and 1 Q8 interval; and 3) sham treatment. In year 2 (beginning at week 56), the 2Q8 group will be treated with a flexible treatment regimen. The primary outcome measure of the study is the proportion of patients who have improved by ≥2 steps from baseline on the DRSS in the combined 2Q8 and 2Q16 groups at week 24, and in each group separately at week 52. Patients will be evaluated for efficacy (best corrected visual acuity [BCVA] using the 4-meter Early Treatment Diabetic Retinopathy Study [ETDRS] protocol, spectral domain optical coherence tomography [SD-OCT], and fluorescein angiography [FA]/fundus photography [FP]) and for ocular and systemic safety (including ophthalmic exams, visual field testing, and laboratory assessments) through week 100. Patients who develop PDR, anterior segment neovascularization (ASNV), or DME in the study eye will qualify for rescue treatment. If treatment is given, patient data will be censored for the primary analysis.

	Intravitreal aflibercept (2 mg) will be made available for patients who have central-involved DME (CI-DME), PDR or ASNV in the fellow eye at screening (beginning on day 1), or are diagnosed during the trial. Standard of care treatment (eg, PRP) will also be allowed for patients developing PDR in the fellow eye at any time during the trial.
Study Duration	The study duration is 103 weeks, including the screening period.
Population	
Sample Size:	Approximately 360 patients will be enrolled, and with a target enrollment of approximately 120 patients in each treatment group (1:1:1 ratio).
Target Population:	The patient population will include men or women with type 1 or 2 diabetes mellitus who have moderately severe to severe NPDR (without DME threatening the center of the macula), in whom PRP can be safely deferred for at least 6 months. For patients who meet eligibility criteria in both eyes, the eye with the most severe DRSS score will be selected as the study eye. If both eyes have equivalent scores, factors such as ocular dominance and patient preference should be considered in making the selection.
Treatments	
Study Drug Dose/Route/Schedule:	The investigational product is intravitreal aflibercept injection (IAI), and will be administered to the patients by IVT injection. **Study Eye** Patients will be randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio: • 2Q8: aflibercept 2 mg Q8 to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with aflibercept 2 mg to week 96 • 2Q16: aflibercept 2 mg Q16 to week 96 (after 3 initial monthly doses and 1 Q8 interval) • Sham: sham injections every 4 weeks (Q4) to week 16, followed by sham injections Q8 to week 96 To preserve the masking, sham injections will be performed for the 2Q8 and 2Q16 groups at treatment visits in which patients do not receive an active injection through week 96, and at all treatment visits for the sham group from baseline to week 96. Masking will be maintained to the end of the study (week 100).
Endpoints	
Primary:	The primary outcome measure of the study is the proportion of patients who have improved by ≥2 steps from baseline in the DRSS score at week 24 in the combined 2Q8 and 2Q16 groups, and at week 52 for each group separately.

Secondary:	The secondary outcome measures will be tested at week 52 and are as follows: • Proportion of patients developing a vision-threatening complication due to diabetic retinopathy **Vision-threatening complications** are defined as composite outcome of PDR (inclusive of patients who have vitreous hemorrhage or tractional retinal detachment believed to be due to PDR) and ASNV o Note: ASNV is defined as neovascularization of the iris (at least 2 cumulative clock hours), and/or definitive neovascularization of the iridocorneal angle • Proportion of patients who develop CI-DME • Time to development of a vision-threatening complication • Time to development of CI-DME • Proportion of patients who receive PRP, inclusive of patients undergoing vitrectomy with endolaser • Area under the curve (AUC) for change in BCVA from baseline These outcome measures will also be tested at week 100 in an exploratory manner for all 3 treatment groups.
Procedures and Assessments	Efficacy and safety ocular procedures will include BCVA (ETDRS) and refraction, intraocular pressure (IOP), slit lamp examination, gonioscopy, indirect ophthalmoscopy, SD-OCT, FA/FP, and visual field testing (study eye). Overall safety will be assessed by evaluation of treatment-emergent adverse events (TEAEs), physical examinations, electrocardiograms (ECGs), vital signs, and clinical safety laboratory tests (hematology, blood chemistry, hemoglobin A1c [HbA1c], and urinalysis) at prespecified time points.
Statistical Plan	The primary efficacy variable is the proportion of patients with a ≥2-step improvement from baseline in DRSS score in the study eye at week 24 in the combined 2Q8 and 2Q16 groups, and at week 52 for the 2Q8 and 2Q16 groups separately. Statistical testing of week 24 and week 52 will be conducted to demonstrate the superiority of the aflibercept groups (combined, 2Q8, and 2Q16) to the sham group, respectively. The primary efficacy variable analysis will be conducted on the full analysis set (FAS) population. The primary analysis is a statistical evaluation of superiority of 3 comparisons (combined aflibercept vs. sham at week 24, aflibercept 2Q8 vs. sham at week 52, and aflibercept 2Q16 vs. sham at week 52) in respect to the primary efficacy variable. The statistical analysis will be performed using the Cochran-Mantel-Haenszel method, stratified by baseline DRSS level (level 47 vs. level 53). Missing or nongradable post-baseline values will be imputed using the last observation carried forward (LOCF) procedure. For any patient who receives rescue treatment, the measurements after rescue is given will be imputed using the

last observation prior to rescue treatment. Baseline values will be carried forward if all post-baseline observations are missing or nongradable.

Aflibercept treatment will be considered to be superior to sham if the estimated aflibercept group (combined, aflibercept 2Q8, or aflibercept 2Q16) is greater than the sham group, and the p-value is less than or equal to or statistically significant at a 1.67% level.

A hierarchical testing procedure will be performed for each dose group to compare the secondary efficacy variables between the respective aflibercept group and the sham group at week 52.

For a sensitivity analysis, the primary efficacy analysis will also be performed using all observed measurements (regardless of whether rescue treatment was given), and only true missing values will be imputed using the LOCF procedure. Baseline values will be carried forward if all post-baseline observations are missing or nongradeable.

Safety Variables

Safety variables will be summarized on the safety analysis set (SAF) through week 24 for the combined 2Q8 and 2Q16 group, and the sham group. Safety data accumulated through week 52 and week 100 for each treatment group will be summarized at the respective time point.

Summaries of all TEAEs by treatment group, and by ocular study eye, ocular fellow eye, and non-ocular TEAEs, will include the number and percentage of patients with at least 1 TEAE. Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Sample Size

Anticipating approximately 41% of patients with a ≥2-step improvement from baseline in DRSS score in either the 2Q8 or 2Q16 groups versus 17% in the sham group, 102 patients per group are required to detect a difference with a power of 90% for rejecting the null hypothesis at a 2-sided 1.67% (5%/3) significance level. A sample size of 102 patients per group will provide at least 90% power to detect a difference between the combined aflibercept group and sham group at week 24, if a 38% response rate is assumed in the combined aflibercept group. To account for about a 15% dropout rate, 120 patients per group will be enrolled.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

2Q4	2 mg every 4 weeks
2Q8	2 mg every 8 weeks
2Q16	2 mg every 16 weeks
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Argus	Pharmacovigilance and clinical safety software system
ASNV	Anterior segment neovascularization
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCVA	Best corrected visual acuity
BUN	Blood urea nitrogen
CI-DME	Central-involved DME
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
DME	Diabetic macular edema
DRSS	Diabetic Retinopathy Severity Scale
ECG	Electrocardiogram
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full analysis set
FP	Fundus photography
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
IAI	Intravitreal aflibercept injection
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IOP	Intraocular pressure
IVT	Intravitreal
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward

MedDRA	Medical Dictionary for Regulatory Activities
NPDR	Nonproliferative diabetic retinopathy
OCT	Optical coherence tomography
PCSV	Potentially clinically significant value
PDR	Proliferative diabetic retinopathy
PRP	Panretinal photocoagulation
PT	Preferred term
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD-OCT	Spectral Domain Optical Coherence Tomography
SMT	Safety monitoring team
SOC	System organ class
TEAE	Treatment-emergent adverse event
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Diabetes mellitus and its complications are a worldwide health epidemic that is expected to increase. In 2013, the World Health Organization estimated that 347 million people had diabetes and this number has been projected to increase to 366 million by 2030 and potentially more if rates of obesity continue to increase (Wild 2004). Despite early intervention programs and better methods of glycemic control, morbidity and mortality as a consequence of diabetes, including diabetic retinopathy, are expected to rise. Diabetic retinopathy is microvascular damage to the blood vessels in the retina, and it can progress to vision-threatening stages including proliferative diabetic retinopathy (PDR), where new vessels that are susceptible to hemorrhage grow initially from the retina and/or optic disc and extend beyond the internal limiting membrane, and diabetic macular edema (DME), where fluid accumulates disrupting the macular architecture and function. Although there are treatments for DME (eg, anti-vascular endothelial growth factor [VEGF] agents), there is a significant unmet medical need for the treatment of diabetic retinopathy. More advanced retinopathy (proliferative) is often treated with panretinal photocoagulation (PRP). Although PRP may stop the progression of a proliferative disease, it is inherently destructive to the retina and, therefore, likely to cause visual symptoms such as visual field defects, reduced contrast sensitivity, and impaired night and color vision, and can also lead to exacerbation of macular edema (Bressler 2011). There is currently no treatment for nonproliferative diabetic retinopathy (NPDR), and patients are observed until disease progresses sufficiently to warrant PRP.

Intravitreal (IVT) anti-VEGF therapy is currently the standard of care treatment for DME, and it has proven to be generally safe and effective in patients with DME. In the phase 3 VISTA and VIVID studies of EYLEA® (aflibercept, known in the scientific literature and in clinical studies as VEGF Trap-Eye or intravitreal aflibercept injection [IAI]), patients treated with either aflibercept 2 mg every 4 weeks (2Q4) or aflibercept 2 mg every 8 weeks (2Q8) (following 5 initial monthly doses) regimens gained 11.5 and 10.7 letters, respectively, in best corrected visual acuity (BCVA) at week 52 (data on file). Similar visual acuity (VA) gains were seen in the RISE and RIDE studies of 0.3 and 0.5 mg Lucentis given monthly (Brown 2013).

In addition to the effect on vision, improvements in diabetic retinopathy as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) were demonstrated in studies of EYLEA and Lucentis. In the VISTA and VIVID studies, the proportion of patients showing a ≥2-step improvement in DRSS at week 52 for the 2Q4 and 2Q8 groups was 33.8% and 29.1% (VISTA) and 33.3% and 27.7% (VIVID), respectively (Korobelnik 2014). In order to confirm that these results would be consistent for a population with moderately severe to severe NPDR at baseline, a subgroup analysis was performed in patients with a baseline DRSS score of level 47 or 53. In this subgroup, as with the entire population, consistently more patients in the aflibercept groups had a ≥2-step improvement in DRSS (2Q4 = 49.6%, 2Q8 = 43.9%), as compared to the laser group (16.7%) (data on file). It is also worth noting that the proportion of patients with ≥2-step improvement in DRSS both in the subgroup and the overall population at week 52 was similar at the earlier time point of week 24.

Despite advances in treatment for DME, there are currently no approved treatments for NPDR in patients without DME, leaving patients at risk for the development of DME and/or PDR. Based on the evidence from the VISTA and VIVID studies in patients with DME showing that EYLEA (in addition to treating macular edema) also improves the underlying diabetic retinopathy, we propose to investigate EYLEA in patients with moderately severe to severe NPDR who do not have DME by assessing the proportion of patients who improve by at least 2 steps on the DRSS.

This phase 3 study will assess the efficacy and safety of IVT aflibercept in patients with moderately severe to severe NPDR.

Additional background information on the study drug can be found in the Investigator's Brochure.

1.2. Rationale

1.2.1. Rationale for Study Design

Patients with severe NPDR may have 20/20 vision and therefore experience no symptoms of their advancing disease. However, profound vision loss can occur acutely if the fragile, leaky vessels develop and either bleed into the vitreous cavity or cause retinal traction and/or detachment (Bressler 2011). Therefore, slowing or halting the worsening of disease will minimize or completely avert these severe, often irreversible, effects on vision in a patient population for which there are no approved, or generally accepted, therapies.

The most comprehensive grading scale that has been developed for diabetic retinopathy was derived from the ETDRS. This was a landmark study that established the value of laser photocoagulation in managing diabetic retinopathy. From this study, a systematic grading scale, the DRSS, was derived to predict progression from NPDR to PDR.

Based on the evidence from the VISTA and VIVID studies showing that aflibercept, in addition to treating macular edema, also improves the underlying diabetic retinopathy in patients with severe NPDR, this study is designed to assess the superiority of aflibercept when compared to sham in treating patients with moderately severe to severe NPDR, by assessing the proportion of patients who improve by at least 2 steps on the DRSS. In the VISTA and VIVID studies, the 2Q8 interval was shown to be effective in improving the DRSS score in patients with macular edema. However, as patients with moderately severe to severe NPDR who do not have concurrent DME are unlikely to be experiencing vision loss, a longer interval between physician visits and injections would be preferable. Therefore, a dosing regimen with a longer interval will be tested (aflibercept 2 mg every 16 weeks [2Q16]) in the current study, along with the 2Q8 regimen.

1.2.2. Rationale for Dose Selection

The 2 mg dose of aflibercept is the same as the currently marketed dose of EYLEA and was used in the phase 3 DME studies, where improvement in underlying diabetic retinopathy was demonstrated.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to assess the efficacy of IVT aflibercept compared to sham treatment in the improvement of moderately severe to severe NPDR.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To characterize the safety of IVT aflibercept in patients with moderately severe to severe NPDR
- To determine if IVT aflibercept will prevent the worsening of diabetic retinopathy and reduce the incidence of DME
- To determine the anatomic effects of IVT aflibercept in patients with moderately severe to severe NPDR

3. STUDY DESIGN

3.1. Study Description and Duration

This is a phase 3, double-masked, randomized study of the efficacy and safety of IVT aflibercept for the improvement of moderately severe to severe NPDR.

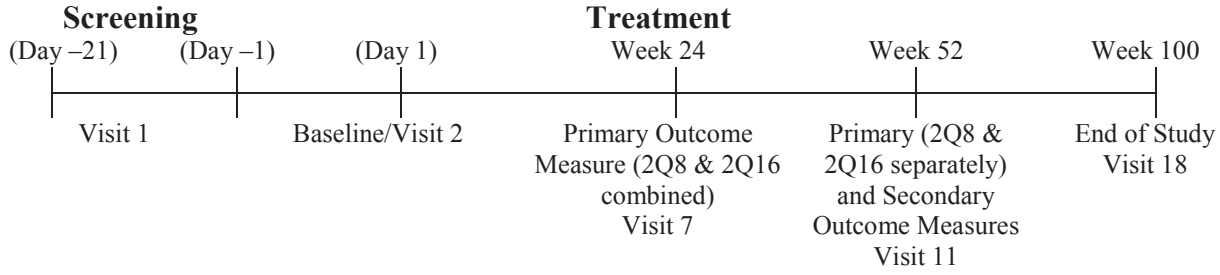
After providing informed consent, patients will be assessed for study eligibility at the screening visit, up to 3 weeks before day 1/baseline. At the day 1/baseline visit, patients will undergo safety assessments prior to receiving the first dose of study drug.

Eligible patients will be enrolled into 1 of 3 treatment groups in a 1:1:1 randomization scheme, and will be stratified based on their DRSS score (level 47 vs. level 53). Only 1 eye will be selected as the study eye. The 3 treatment groups will have the following dosing regimens from day 1 to week 48: 1) 2Q8 aflibercept IVT after 5 initial monthly doses; 2) 2Q16 aflibercept IVT after 3 initial monthly doses and 1 8-week interval; and 3) sham treatment (see section 5.1). In year 2 (beginning at week 56), the 2Q8 group will be treated with a flexible treatment regimen (see section 5.3).

The primary outcome measure of the study is the proportion of patients who have improved by ≥2 steps from baseline on the DRSS in the combined 2Q8 and 2Q16 groups at week 24, and in each group separately at week 52. Patients will be evaluated for efficacy (BCVA using the 4-meter ETDRS protocol, spectral domain optical coherence tomography [SD-OCT], and fluorescein angiography [FA]/fundus photography [FP]) and for ocular and systemic safety (including ophthalmic exams, visual field testing, and laboratory assessments) through week 100 (Figure 1).

Patients who develop PDR, anterior segment neovascularization (ASNV), or DME will qualify for rescue treatment (see section 5.2). If treatment is given, patient data will be censored for the primary analysis.

Figure 1: Study Flow Diagram



3.2. Planned Interim Analysis

No formal interim analysis is planned.

3.3. Study Committees

3.3.1. Safety Monitoring Team

A safety monitoring team (SMT) at Regeneron will meet at scheduled times during the study to review masked safety data. These data may include, but are not limited to:

- Treatment-emergent adverse events (TEAEs) that result in an early study withdrawal
- Serious adverse events (SAEs)
- Fatal events
- Identified and potential risks for IVT aflibercept

Appropriate action, if needed, will be taken based upon these reviews and in consultation with the medical monitor.

3.3.2. Other Safety Committee

Potential arterial thrombotic events will be evaluated by a masked adjudication committee according to criteria formerly applied and published by the Anti-Platelet Trialists' Collaboration prior to database unmasking (Antithrombotic Trialists' Collaboration 1994; Antithrombotic Trialists' Collaboration 2002). An arterial thrombotic event is defined as a nonfatal myocardial infarction, nonfatal ischemic stroke, nonfatal hemorrhagic stroke, or death resulting from vascular or unknown causes. Additional details regarding data to be collected can be found in the study procedure manual.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Approximately 360 patients will be enrolled in approximately 70 sites, with a target enrollment of approximately 120 patients in each treatment group.

4.2. Study Population

The patient population will include men or women with type 1 or 2 diabetes mellitus who have moderately severe to severe NPDR (without DME threatening the center of the macula), in whom PRP can be safely deferred for at least 6 months.

For patients who meet eligibility criteria in both eyes, the eye with the most severe DRSS score will be selected as the study eye. If both eyes have equivalent scores, factors such as ocular dominance and patient preference should be considered in making the selection.

4.2.1. Inclusion Criteria

A patient must meet the following criteria at screening and at day 1 to be eligible for inclusion in the study:

1. Men or women ≥18 years of age with type 1 or 2 diabetes mellitus who have moderately severe to severe NPDR (DRSS levels 47 or 53), confirmed by the central reading center, in whom PRP can be safely deferred for at least 6 months per the investigator
2. BCVA ETDRS letter score in the study eye of ≥69 letters (approximate Snellen equivalent of 20/40 or better)
3. Willing and able to comply with clinic visits and study-related procedures
4. Provide signed informed consent

4.2.2. Exclusion Criteria

A patient who meets any of the following criteria at either the screening visit or at day 1 will be excluded from the study:

1. Presence of DME threatening the center of the macula (within 1,000 microns of the foveal center) in the study eye
2. Evidence of retinal neovascularization on clinical examination or FA
3. Any prior focal or grid laser photocoagulation (within 1,000 microns of the foveal center) or any prior PRP in the study eye
4. Any prior systemic anti-VEGF treatment or IVT anti-VEGF treatment in the study eye
5. Any prior intraocular steroid injection in the study eye
6. History of vitreoretinal surgery in the study eye
7. Intraocular pressure (IOP) ≥25 mm Hg in the study eye

8. Evidence of active infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye
9. Any intraocular inflammation or infection in either eye within 3 months of the screening visit
10. Current ASNV, vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in the study eye
11. Ocular media of insufficient quality to obtain fundus and optical coherence tomography (OCT) images in the study eye
12. Hemoglobin A1c (HbA1c) >12%, or if HbA1c is ≤12%, diabetes mellitus is uncontrolled in the opinion of the investigator
13. Uncontrolled blood pressure (defined as systolic >160 mm Hg or diastolic >95 mm Hg while patient is sitting)
14. History of cerebrovascular accident or myocardial infarction within 180 days of day 1
15. Renal failure, dialysis, or history of renal transplant
16. Women who are breastfeeding or who have a positive serum hCG/urine pregnancy test at the screening or baseline visit
17. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of IVT injections, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety
18. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications
19. Participation as a patient in any interventional clinical study within the 12 weeks prior to day 1 of the study
20. Sexually active men* or women of childbearing potential** who are unwilling to practice adequate contraception prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last dose. 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; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly.

    * Contraception is not required for men with documented vasectomy.

    ** Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.
21. Patients who are on systemic anti-VEGF treatment (ie, bevacizumab, ziv-aflibercept) for oncology treatment (if a patient requires systemic anti-VEGF treatment during the study, the patient will be withdrawn)

4.3. Premature Withdrawal from the Study

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

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

Patients who withdraw prematurely from the study will be asked to complete study assessments per section 6.2.1.

4.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

The investigational product is IAI, which will be supplied in sterile, sealed, 3 mL, single-use vials, each with a "withdrawable" volume of approximately 50 µL (0.05 mL) at a concentration of 40 mg/mL.

The injection volume will be 50 µL (0.05 mL) and will be administered to the patients by IVT injection. Only 1 eye will be selected as the study eye.

Study Eye

Patients will be randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio:

- 2Q8: aflibercept 2 mg Q8 to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with aflibercept 2 mg to week 96
- 2Q16: aflibercept 2 mg Q16 to week 96 (after 3 initial monthly doses and 1 8-week interval)
- Sham: sham injections Q4 to week 16, followed by sham injections Q8 to week 96

Masking will be maintained to the end of the study (week 100). To preserve the masking, sham injections will be performed for the 2Q8 and 2Q16 groups at treatment visits in which patients do not receive an active injection through week 96, and at all treatment visits for the sham group from baseline to week 96. Instructions on dose preparation are provided in the pharmacy manual.

5.2. Rescue Treatment in the Study Eye

Patients who develop PDR, ASNV, or central-involved DME (CI-DME) in the study eye may be treated, if deemed appropriate by the masked physician. For any of these complications, an FP must be performed before rescue treatment is given.

Patients who develop CI-DME may receive IVT aflibercept (refer to EYLEA USPI 2015) or laser photocoagulation, and will no longer receive their randomized treatment. Rescue treatment may be given by the masked or unmasked physician.

Patients who develop PDR and/or ASNV may receive PRP or vitrectomy with endolaser, if necessary, but will remain on their randomized treatment schedule. Panretinal photocoagulation or surgical intervention may be performed by either the masked or unmasked physician. In addition, 1 injection of aflibercept may be given, which must be administered by the unmasked physician.

If treatment for DME, ASNV, or PDR is given, patient data will be censored from the time of treatment for the primary analysis.

5.3. Flexible Treatment in the 2Q8 Group in the Study Eye

Beginning at week 56, patients randomized to the 2Q8 group will receive aflibercept using a flexible treatment regimen. An injection will be given at each visit unless a patient has reached Level 35 or better (mild NPDR) on the DRSS (as determined by the masked investigator), at which point treatment will be deferred (and a sham injection given). Level 35 can be clinically defined as microaneurysms plus venous loops, hard exudates, cotton wool spots, and/or mild retinal hemorrhages (less than present in ETDRS standard photograph 2a in up to 3 quadrants [see also study procedure manual]). The determination whether Level 35 or better has been reached will be assessed by the masked investigator at each visit on FP.

To maintain masking, all treatment groups will be assessed (using FP) for flexible treatment criteria from week 56 to week 96, but the 2Q16 group will continue to receive treatment every 16 weeks and the sham group will continue to receive sham injections at every visit.

5.4. Dose Modification and Study Drug Discontinuation Rules

5.4.1. Dose Modification

Dose modification for an individual patient is not allowed.

5.4.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who opt to withdraw from the study will be asked to complete study assessments, per section 6.2.1.

5.5. Method of Treatment Assignment

Approximately 360 patients will be randomized in a 1:1:1 ratio to receive either aflibercept 2Q8, aflibercept 2Q16, or sham according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified according to the patient's DRSS level (level 47 vs. level 53 at the screening visit).

5.5.1. Masking

To preserve the masking, sham injections will be performed for the 2Q8 and 2Q16 groups at treatment visits in which patients do not receive an active injection through week 96; sham injections will be performed at all treatment visits for the sham group from baseline to week 96. Weeks 52 and 100 are nontreatment visits.

A masked physician will be assigned to do the following: 1) assess AEs, and 2) perform the masked assessment of efficacy. A separate, unmasked physician will administer treatment in the study eye (ie, perform study drug injection or sham injection) (Table 1).

The unmasked physician or designee will not have any role in the study beyond the receipt, tracking, preparation, destruction, administration of study drug, and assessing safety during the observation period following study drug administration. The masked physician will determine if a patient has developed DME, ASNV, or PDR in the study eye, and will be responsible for recommending treatment, which will be administered by the unmasked physician. Once it has been determined that a patient has progressed to DME, ASNV, or PDR, treatment may be given by either the masked or unmasked physician. Beginning at week 56, the masked physician will assess whether a patient has a DRSS Level 35 or better in the study eye using FP, to determine the need for flexible treatment. The unmasked physician will administer sham or active treatment per protocol.

Every effort must be made to ensure that all other study site personnel other than those designated as unmasked remain masked to treatment assignment.

Masked and unmasked roles will be assumed for the entire study, and switching from an unmasked to a masked role after the first patient is randomized at a site is not permitted. Any deviation to the roles above must first be approved by the sponsor. This must be properly documented before any patients are treated, and the Site Signature and Delegation Log must be maintained as new personnel are added to the study team.

Table 1: Responsibilities of the Masked and Unmasked Personnel

Masked or Unmasked Personnel
• Performs all screening procedures up until randomization • Assesses inclusion/exclusion criteria • Obtains medical/ophthalmic history • Obtains informed consent • Collects samples for laboratory testing and antibody sampling • Performs electrocardiograms (ECGs) and transfers to reading center • Administers rescue treatment once the need for rescue has been determined by the masked investigator (physician only)
Masked Personnel
• Determines if a patient has developed DME, ASNV, or PDR in the study eye and recommends treatment (physician only) • Assesses AEs, including severity and relationship • Assesses efficacy • Performs ophthalmic examinations, including IOP, at all study visits (except post-dose examinations immediately after treatment) • Evaluates all safety, including review of images for safety concerns (except those immediately after IVT injection) • May perform fellow eye injections at any unscheduled visits where only the fellow eye is treated • Tests refraction and BCVA (no exceptions will be granted) • Performs Humphrey Visual Field test • Performs and assesses OCT, FP, and FA images and transfers them to reading centers • Assesses need for flexible treatment during year 2
Unmasked Personnel
• Coordinates randomization • Performs receipt and accountability of study drug • Performs study drug (IAI) or sham injection (study eye) • Performs fellow eye injection (if treatment is administered bilaterally/in conjunction with study eye treatment) • Observes safety at the end of the observation period (approximately 30 minutes following study treatment) • Checks IOP post-dose (study eye) before the end of the approximately 30-minute observation period • Checks indirect ophthalmoscopy post-dose (study eye)

After the week 24 and week 52 analyses, study reports will be issued that will indicate the efficacy outcomes up to week 24 and week 52, respectively. All patients and study personnel who were masked through week 24 and week 52 will remain masked to the individual patient treatment assignments even after the issuance of each study report, respectively.

5.5.2. Emergency Unmasking

Unmasking of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy).

- If unmasking is required:
  - Only the investigator will make the decision to unmask the treatment assignment.
  - Only the affected patient will be unmasked.
  - Unmasking of the treatment assignment must be performed via the IVRS; manual unmasking (ie, via the designated unmasked staff at the study site) will not be permitted
  - The investigator will notify Regeneron and/or designee before unmasking the patient, whenever possible

If emergency unmasking is required and the IVRS is not available, only the Regeneron Head of Pharmacovigilance and Risk Management or designee will unmask the patient and provide the treatment assignment to the investigator.

5.6. Treatment Logistics and Accountability

[redacted]

5.6.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient,
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

Drug accountability will be also performed for aflibercept administered in the fellow eye.

5.6.4. Treatment Compliance

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

5.7. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

If a pretreatment concomitant medication is administered in the study eye before injection (eg, antibiotic or anesthetic), it must be administered for both active and sham treatment.

5.7.1. Prohibited Medications and Procedures

Patients may not receive any medications (approved or investigational) for their diabetic retinopathy in the study eye other than the assigned study treatment (aflibercept or sham) as specified in this protocol, unless they have developed PDR, ASNV, or DME (in which case they may be treated as indicated in section 5.2) or completed the end of study (week 100) visit assessments. This includes medications administered locally (eg, IVT, topical, juxtascleral or periorbital routes), as well as those administered systemically, with the intent of treating the study and/or fellow eye.

Aflibercept will be provided for fellow eye use (see section 5.7.2); other anti-VEGF agents will not be allowed.

5.7.2. Permitted Medications and Procedures

Fellow Eye

Intravitreal aflibercept (2 mg) will be made available for patients who have CI-DME, PDR or ASNV in the fellow eye at study start (beginning on day 1), or are diagnosed during the trial (refer to EYLEA USPI 2015).

Standard of care treatment (eg, PRP) will also be allowed for patients developing PDR in the fellow eye at any time during the trial.

The patient's fellow eye may receive treatment on the same day as the study eye or at an unscheduled visit. All fellow eye treatments must be recorded on the electronic case report form (CRF) as a concomitant medication and/or procedure for the fellow eye. The fellow eye will not be considered an additional study eye. Patients who receive treatment for the fellow eye will not be required to be withdrawn from the study. Safety of the fellow eye will be monitored and all AEs will be collected. Other conditions in the fellow eye may be treated with approved therapies.

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

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

6.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 2 and Table 3.

Additional details for the exploratory OCT-angiography sub-study are provided in Appendix 1.

Table 2: Schedule of Events – Year 1

Study Procedure	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Year 1 Treatment Period Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11[1]
Week	--	0	4	8	12	16	24	32	40	48	52
Day (visit window)	-21 to -1	1	29 ± 7 days	57 ± 7 days	85 ± 7 days	113 ± 7 days	169 ± 7 days	225 ± 7 days	281 ± 7 days	337 ± 7 days	365 ± 10 days
Screening/Baseline:											
Informed consent	X										
[redacted]	[redacted]										
Inclusion/exclusion	X	X									
Medical and ophthalmic history	X										
Demographics	X										
Randomization		X									
Treatment:											
Review of concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Administer IVT aflibercept (IAI) or sham[2]		X	X	X	X	X	X	X	X	X	
Ocular Assessments:											
BCVA (ETDRS) and refraction	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy[3]	X				X		X		X		X
Intraocular pressure[4]	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[5]	X	X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X
FA & FP[6]	X			X[7]	X		X		X		X
Visual field testing (study eye)[8]	X[9]										X

Study Procedure	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Year 1 Treatment Period: Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11[1]
Week	--	0	4	8	12	16	24	32	40	48	52
Day (visit window)	-21 to -1	1	29 ± 7 days	57 ± 7 days	85 ± 7 days	113 ± 7 days	169 ± 7 days	225 ± 7 days	281 ± 7 days	337 ± 7 days	365 ± 10 days
Non-Ocular Assessments:											
Physical examination	X[10]										
Vital signs[11]	X	X	X	X	X	X	X	X	X	X	X
ECG	X										X
Adverse events[12]	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:[13]											
Hematology, blood chemistry, urinalysis, Vitamin D and HbA1c[14]	X						X[15]				X
Pregnancy test, women of childbearing potential[16]	serum	urine	urine	urine	urine	urine	urine	urine	urine	urine	
Anti-aflibercept antibody samples[17]		X									X
[redacted]		[redacted]									

1. Patients who are withdrawn from the study before week 52/visit 11 will be asked to return to the clinic to complete the visit 11 assessments.
2. Patients will receive either IAI or sham injections given by the unmasked investigator, depending on the assigned treatment group.
3. Gonioscopy in the study eye only.
4. Intraocular pressure will be measured pre-dose (bilateral) and approximately 30 minutes after administration of study drug on days when study drug/sham is administered (study eye only).
5. Indirect ophthalmoscopy will be performed pre-dose (bilateral) and immediately after administration of study drug on days when study drug is administered (study eye only).
6. An FP must be performed once a patient has been diagnosed with PDR, ASNV, or CI-DME in the study eye, and before rescue treatment is given. For sites that will capture FA images on the Optos® Ultra-Widefield Imaging system, axial length must be measured in both eyes at baseline using any appropriate method.
7. Only FP at week 8.
8. Only sites that have access to Humphrey Visual Field will perform visual field testing at the indicated visits.
9. May be performed at visit 1 or visit 2.
10. Including height and weight.
11. Vital signs (body temperature, blood pressure, and heart rate) will be measured after the patient has been sitting for 5 minutes.
12. Adverse events will be collected from the time the informed consent form (ICF) is signed until early termination or the end of study visit. If a patient withdraws from the study, ongoing AEs will be followed to the end of study visit or until the patient withdraws consent.

13. All samples collected for laboratory assessments will be obtained prior to administration of study drug.
14. At visits at which FA is performed, urinalysis samples will be collected before FA in order to avoid false elevations in urine protein values. Vitamin D will be tested at visit 1 (screening) only.
15. Sampling only for HbA1c.
16. For women of childbearing potential, a negative screening serum pregnancy test and urine pregnancy test on day 1 are required before randomization. All women of childbearing potential will have a urine pregnancy test at each treatment visit starting at visit 2 (day 1); a negative urine pregnancy test is required before treatment is administered (randomized treatment, rescue treatment with IAI, or fellow eye treatment with IAI).
17. All ADA samples must be collected prior to administration of study drug on days when study drug is administered.

[redacted]

Table 3: Schedule of Events – Year 2

Study Procedure	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18/End of Study[1]
Week	56	64	72	80	88	96	100
Day (visit window)	393 ± 7 days	449 ± 7 days	505 ± 7 days	561 ± 7 days	617 ± 7 days	673 ± 7 days	701 ± 10 days
Treatment:							
Review of concomitant medications	X	X	X	X	X	X	X
Administer IVT aflibercept (IAI) or sham[2]	X	X	X	X	X	X	
Ocular Assessments:							
BCVA (ETDRS) and refraction	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X
Gonioscopy[3]		X		X			X
Intraocular pressure[4]	X	X	X	X	X	X	X
Indirect ophthalmoscopy[5]	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X
FP[6]	X	X	X	X	X	X	X
FA[7]		X		X			X
Visual field testing (study eye)[8]							X
Non-Ocular Assessments:							
Vital signs[9]	X	X	X	X	X	X	X
ECG							X
Adverse events[10]	X	X	X	X	X	X	X

Study Procedure	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18/End of Study[1]
Week	56	64	72	80	88	96	100
Day (visit window)	393 ± 7 days	449 ± 7 days	505 ± 7 days	561 ± 7 days	617 ± 7 days	673 ± 7 days	701 ± 10 days
Laboratory Testing:[11]							
Hematology, blood chemistry, urinalysis, Vitamin D, and HbA1c[12]							X
Pregnancy test, women of childbearing potential[13]	urine	urine	urine	urine	urine	urine	urine
Anti-aflibercept antibody samples[14]							X
[redacted]							

1. Patients who are withdrawn from the study after week 52/visit 11 will be asked to return to the clinic for week 100/visit 18 assessments.
2. Patients will receive either IAI or sham injections given by the unmasked investigator, depending on the assigned treatment group.
3. Gonioscopy in the study eye only.
4. Intraocular pressure will be measured pre-dose (bilateral) and approximately 30 minutes after administration of study drug on days when study drug/sham is administered (study eye only).
5. Indirect ophthalmoscopy will be performed pre-dose (bilateral) and immediately after administration of study drug on days when study drug is administered (study eye only).
6. An FP must also be performed once a patient has been diagnosed with PDR, ASNV, or CI-DME in the study eye, and before rescue treatment is given.
7. For sites that will capture FA images on the Optos® Ultra-Widefield Imaging system, axial length must be measured in both eyes at baseline using any appropriate method.
8. Only sites that have access to Humphrey Visual Field will perform visual field testing at the indicated visits.
9. Vital signs (body temperature, blood pressure, and heart rate) will be measured after the patient has been sitting for 5 minutes.
10. Adverse events will be collected from the time the ICF is signed until early termination or the end of study visit. If a patient withdraws from the study, ongoing AEs will be followed to the end of study visit or until the patient withdraws consent.
11. All samples collected for laboratory assessments should be obtained prior to administration of study drug.
12. At visits at which FA is performed, urinalysis samples will be collected before FA in order to avoid false elevations in urine protein values. Vitamin D will be tested at visit 18 (week 100) only.
13. All women of childbearing potential will have a urine pregnancy test at each treatment visit starting at visit 2 (day 1). A negative urine pregnancy test is required before treatment is administered (randomized treatment, rescue treatment with IAI, or fellow eye treatment with IAI)
14. All ADA samples must be collected prior to administration of study drug on days when study drug is administered.

[redacted]

6.2. Study Visit Descriptions

6.2.1. Early Termination Visit

Patients who are withdrawn from the study before week 52/visit 11 will be asked to return to the clinic to complete the visit 11 assessments, as described in Table 2. Patients who are withdrawn from the study after week 52/visit 11 will be asked to return to the clinic for week 100/visit 18 assessments, as described in Table 3.

6.2.2. Unscheduled Visits

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

6.3. Study Procedures

6.3.1. Procedures Performed Only at the Screening/Baseline Visit

For women of childbearing potential, a negative serum pregnancy test at screening is required for eligibility.

6.3.2. Ocular Procedures (Efficacy and Safety)

6.3.2.1. Best Corrected Visual Acuity

Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group 1985) at 4 meters at each study visit, as specified in Table 2 and Table 3. Visual acuity examiners must be certified to ensure consistent measurement of BCVA. The VA examiner must remain masked to treatment assignment. Best corrected visual acuity should be done before any other ocular procedures are performed. A detailed protocol for conducting VA testing and refraction can be found in the study procedure manual.

6.3.2.2. Intraocular Pressure

Intraocular pressure of the study eye will be measured at every visit using Goldmann applanation tonometry or Tono-pen™, as specified in Table 2 and Table 3. The same method of IOP measurement must be used throughout the study for each individual patient. Intraocular pressure will be measured pre-dose (bilateral) by the masked physician (or designee), and at approximately 30 minutes post-dose (study eye) by the unmasked physician (or designee).

6.3.2.3. Slit Lamp Examination

Patients' anterior eye structure and ocular adnexa will be examined bilaterally pre-dose at each study visit using a slit lamp (study procedure manual) by the masked investigator, as specified in Table 2 and Table 3.

6.3.2.4. Gonioscopy

Patients will be evaluated for the development of neovascularization of the iridocorneal angle by gonioscopy in conjunction with slit lamp biomicroscopy. The examination should be performed in the study eye only before the application of mydriatic agents, as specified in Table 2 and Table 3, or if frank rubeosis is present.

6.3.2.5. Indirect Ophthalmoscopy

Patients' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre-dose (bilateral) by the masked investigator and post-dose (study eye) by the unmasked investigator, as specified in Table 2 and Table 3. Post-dose evaluation must be performed immediately after injection (active drug or sham).

6.3.2.6. Fundus Photography/Fluorescein Angiography

The anatomical state of the retinal vasculature and the DRSS level will be evaluated by FA and FP as specified in Table 2 and Table 3. The study eye will be the transit eye. Fundus photography and FA will be captured and transmitted to an independent reading center for both eyes.

An FP must be performed once a patient has been diagnosed with PDR, ASNV, or CI-DME in the study eye, and before rescue treatment is given.

Fundus and angiographic images will be sent to an independent reading center where images will be read by masked readers. All FPs and FAs will be archived at the site as part of the source documentation. Photographers must be certified by the reading center to ensure consistency and quality in image acquisition. Every effort will be made to ensure that all photographers at the site remain masked to treatment assignment. A detailed protocol for image acquisition and transmission can be found in the study procedure manual.

For sites that will capture FA images on the Optos® Ultra-Widefield Imaging system, axial length must be measured in both eyes at baseline using any appropriate method.

6.3.2.7. Spectral Domain Optical Coherence Tomography

Retinal characteristics will be evaluated at every visit using SD-OCT. Images will be captured and transmitted for both eyes. Images will be sent to an independent reading center where they will be read by masked readers. All OCTs will be electronically archived at the study sites as part of the source documentation. Optical coherence tomography technicians must be certified by the reading center to ensure consistency and quality in image acquisition. Every effort will be made to ensure that OCT technicians at the study site remain masked to treatment assignment. A detailed protocol for acceptable OCT machines and OCT image acquisition/transmission can be found in the study procedure manual.

Details on an optional sub-study evaluating an exploratory OCT-angiography procedure are provided in Appendix 1.

6.3.2.8. Visual Field Testing

Visual field testing will be assessed in the study eye using the Humphrey Visual Field Analyzer by sites who have access to this machine, at visits specified in Table 2 and Table 3. The first visual field testing may be performed at either visit 1 or visit 2. Technicians must be certified to ensure consistency and quality testing procedures. Every effort will be made to ensure that visual field technicians at the study site remain masked to treatment assignment. A detailed protocol for visual field testing can be found in the study procedure manual.

6.3.3. Safety Procedures (Non-Ocular)

6.3.3.1. Vital Signs

Vital signs, including body temperature, blood pressure, and heart rate will be collected pre-dose at time points according to Table 2 and Table 3. Vital sign measurements will be taken once the patient has been sitting down for 5 minutes.

6.3.3.2. Physical Examination

A physical examination, including height and weight, will be performed at the screening visit.

6.3.3.3. Electrocardiogram

A standard 12-lead ECG measurement will be measured at visits specified in Table 2 and Table 3. Heart rate will be recorded from the ventricular rate and the PR, QRS, RR and QT intervals will be recorded. The ECG strips or report will be retained with the source documentation. Electrocardiograms will be forwarded to a central reader.

6.3.3.4. Laboratory Testing

Hematology, blood chemistry, urinalysis, HbA1c, and pregnancy testing samples will be analyzed by a central laboratory. All samples collected for laboratory assessments will be obtained prior to administration of study drug. At visits at which FA is performed, urinalysis samples must be collected before FA to avoid false elevations in urine protein values. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at time points according to Table 2 and Table 3. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN)	Uric acid
Carbon dioxide	Aspartate aminotransferase (AST)	Creatine phosphokinase (CPK)
Calcium	Alanine aminotransferase (ALT)	
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Urine protein:creatinine ratio	RBC
Clarity	Glucose	Hyaline and other casts
Creatinine	Blood	Bacteria
pH	Bilirubin	Epithelial cells
Specific gravity	Leukocyte esterase	Crystals
Ketones	Nitrite	Yeast
Protein	WBC	

Other Laboratory Tests

Hemoglobin A1c and Vitamin D will be measured at time points according to Table 2 and Table 3.

Women of childbearing potential must have the outcome of their serum pregnancy test before randomization. They should continue to be tested for pregnancy (urine pregnancy test) during the study at every treatment visit. For patients on an IAI rescue regimen, or those being treated with IAI in the fellow eye, urine pregnancy test should be done before each dose.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the masked investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the masked investigator.

Criteria for reporting laboratory values as an AE are provided in section 7.2.5.

6.3.4. Anti-Drug Antibody Procedures

6.3.4.1. Anti-Drug Antibody Measurements and Samples

Samples for anti-drug antibody (ADA) assessment will be collected at time points listed in Table 2 and Table 3. Samples should be collected prior to the administration of study drug. Samples collected for ADA measurements may be used for exploratory analysis or to investigate unexpected AEs.

[redacted]

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 (ie, any clinically significant change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study drug.

7.1.2. Serious Adverse Event

An 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 (eg, 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 (eg, 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).

An ocular important medical event may include the following:

- An AE that requires either surgical or medical intervention to prevent permanent loss of vision
- Substantial, unexplained vision loss or an AE that causes substantial vision loss

7.2. Recording and Reporting Adverse Events

7.2.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study. Refer to the study procedure manual for the procedures to be followed.

Information on follow-up for AEs is provided in section 7.2.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in section 7.2.5.

7.2.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug must be reported to the sponsor (or designee) within 24 hours. Refer to the study procedure manual for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

The investigator must promptly report to the Institutional Review Board (IRB) all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB, regardless of assessed causality.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study/early termination visit - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

7.2.3. Other Events that Require Accelerated Reporting

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE,

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), by telephone within 24 hours of identification, any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 90 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE.

Refer to the study procedure manual for the procedures to be followed.

7.2.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the study procedure manual for the procedures to be followed.

7.2.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- 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

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

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.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in section 7.3.1.

7.2.6. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected 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 AEs will be graded according to the following scale:

- **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

Relationship of AEs to Study Drug:

The relationship of AEs to study drug will be assessed by the masked investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

For a list of factors to consider in assessing the relationship of AEs to study drug, see Appendix 2.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

Relationship of AEs to Injection Procedure:

The relationship of AEs to injection procedure will be assessed by the masked investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the injection procedure?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the injection procedure

Related: There is a reasonable possibility that the event may have been caused by the injection procedure

For a list of factors to consider in assessing the relationship of AEs to the injection procedure, see Appendix 2.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

7.4. Safety Monitoring

The investigator will monitor the safety of study patients at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound. The study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

7.5. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the medicinal/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 patient.

8.2. Primary and Secondary Variables

The primary outcome measure of the study is the proportion of patients who have improved by ≥2 steps from baseline in the DRSS score at week 24 in the combined 2Q8 and 2Q16 groups, and at week 52 for each group separately.

The secondary outcome measures will be tested at week 52 and are as follows:

- Proportion of patients developing a vision-threatening complication due to diabetic retinopathy
  Vision-threatening complications are defined as composite outcome of PDR (inclusive of patients who have vitreous hemorrhage or tractional retinal detachment believed to be due to PDR) and ASNV
  - **Note:** ASNV is defined as neovascularization of the iris (at least 2 cumulative clock hours), and/or definitive neovascularization of the iridocorneal angle
- Proportion of patients who develop CI-DME
- Time to development of a vision-threatening complication
- Time to development of CI-DME
- Proportion of patients who receive PRP, inclusive of patients undergoing vitrectomy with endolaser
- Area under the curve (AUC) for change in BCVA from baseline

See section 9.5.2.1 for hierarchy of endpoints to be tested. These outcome measures will also be tested at week 100 in an exploratory manner for all 3 treatment groups.

8.3. Additional Variables

The additional outcome measures in the study are:

- Time to first improvement of ≥2 steps from baseline in the DRSS score through week 52 and week 100
- Proportion of patients with ≥2-step improvement from baseline in the DRSS score at week 100
- Proportion of patients with ≥2-step worsening from baseline in the DRSS score at week 52 and at week 100
- Proportion of patients with ≥3-step worsening from baseline in the DRSS score at week 52 and at week 100
- Proportion of patients with ≥3-step improvement from baseline in the DRSS score at week 52 and at week 100
- Proportion of patients who receive vitrectomy through week 52 and through week 100
- Change in central retinal thickness from baseline at week 52 and at week 100
- Change in mean deviation on visual field testing from baseline at week 52 and at week 100
- Change in BCVA from baseline at week 52 and week 100
- Proportion of patients who have gained or lost ≥5, ≥10, or ≥15 letters from baseline at week 52 and at week 100
- The proportion of patients who are equal to or better than 20/20 or equal to or better than 20/40 at week 52 and at week 100

The following additional variables will be tested only at the week 24 time point:

- Change in BCVA from baseline at week 24
- AUC for change in BCVA from baseline at week 24
- Proportion of patients who have lost ≥5, ≥10, or ≥15 letters from baseline at week 24

9. STATISTICAL PLAN

This section provides the basis for the SAP for the study. Analysis variables are listed in section 8.

9.1. Statistical Hypothesis

This study will examine the following hypotheses for the primary efficacy variable regarding the proportion of patients with a ≥2-step improvement from baseline in DRSS score in the study eye at week 24 in the combined 2Q8 and 2Q16 groups, and at week 52 for the 2Q8 and 2Q16 groups separately. Statistical testing of week 24 and week 52 will be conducted to demonstrate the superiority of the aflibercept groups (combined, 2Q8, and 2Q16) to the sham group, respectively.

For each test, let p_t (and p_c) be the true proportion of patients with a ≥2-step improvement from baseline in DRSS score at week 24 for the combined 2Q8 and 2Q16 groups, and at week 52 for the 2Q8 and 2Q16 groups separately (and the sham group, p_c).

The following hypotheses will be tested:

H_0: $p_t = p_c$ versus H_1: $p_t \neq p_c$

To control the family-wise type I error rate of 5%, primary efficacy endpoints for the combined group (week 24) and endpoints for the 2Q8 and 2Q16 groups (week 52) will be tested separately at the significance level of $\alpha = 1.67\%$ (5%/3). Secondary efficacy endpoints at week 52 will be tested for the 2Q8 and 2Q16 groups by the hierarchical testing procedure at the significance level for the different scenarios indicated in Table 4.

Table 4: Significance Levels for Testing Secondary Efficacy Endpoints

Scenario	1	2	3	4	5	6	7
Combined Group at Week 24 Positive?	X	X	X		X		
2Q8 Group at Week 52 Positive?	X	X		X		X	
2Q16 Group at Week 52 Positive?	X		X	X			X
Significance level for secondary endpoints	0.05	0.033	0.033	0.033		0.0167	0.0167
Significance level for Testing for 2Q8 Group at week 52	0.025	0.033		0.0167		0.0167	
Significance level for Testing for 2Q16 at week 52	0.025		0.033	0.0167			0.0167

9.2. Justification of Sample Size

Anticipating approximately 41% of patients with a ≥2-step improvement from baseline in DRSS score in either the 2Q8 or 2Q16 groups versus 17% in the sham group, 102 patients per group are required to detect a difference with a power of 90% for rejecting the null hypothesis at a 2-sided 1.67% (5%/3) significance level. A sample size of 102 patients per group will provide at least 90% power to detect a difference between the combined aflibercept group and sham group at week 24, if a 38% response rate is assumed in the combined aflibercept group. The assumption of the proportions for the aflibercept group and sham group is based on VIVID and VISTA data at a given time point. To account for about a 15% dropout rate, 120 patients per group will be enrolled.

The sample size calculation was computed using the Chi square test (continuity corrected) from the commercial software nQuery nTerm 7.0.

9.3. Analysis Sets

9.3.1. Efficacy Analysis Sets

Full analysis set (FAS): The FAS will include all randomized patients who received any study treatment. The analysis on the FAS will be performed according to the treatment assigned at baseline (as randomized).

9.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study treatment (active or sham); it is based on the randomized treatment. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

9.4. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

9.5. Statistical Methods

The statistical methods summarized in this section outline the plan for data analysis of this study. A final and complete SAP will be provided prior to the unmasking of the data.

Unless stated otherwise, all variables will be analyzed descriptively with appropriate statistical methods: continuous variables by sample statistics (ie, mean, standard deviation, median, quartiles, minimum, and maximum), and categorical variables by frequencies and percentages.

All statistical analyses will be performed using Statistical Analysis System (SAS); the version used will be specified in the SAP.

9.5.1. Demography and Baseline Characteristics

Demographic variables and baseline characteristics will be summarized by treatment group and pooled aflibercept treatment groups for the FAS and SAF, depending on the type of data, as described in section 9.5. Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA®) codes, and prior and concomitant medications by Anatomical Therapeutic Chemical (ATC) codes (World Health Organization Drug Dictionary). No formal comparison between treatment groups will be conducted.

Demographic and baseline characteristics will be summarized descriptively by treatment group.

9.5.2. Efficacy Analyses

Efficacy analyses of all efficacy variables defined in section 8.2 will be conducted using the FAS population. Missing values will be imputed with post-baseline values during the ontreatment period by using the last observation carry forward (LOCF) procedure. For any patient who receives rescue treatment, measurements after rescue is given will be imputed using the last observation prior to rescue treatment.

The primary endpoint analysis for the study will be conducted at 2 time points (week 24 for the combined 2Q8 and 2Q16 groups, and week 52 for the 2Q8 and 2Q16 groups separately). Each of the primary efficacy analyses will be tested at the 1.67% (5%/3) significance level to control for multiplicity.

The secondary endpoints described in section 8.2 for both groups (2Q8 and 2Q16) will be tested in a hierarchical manner at week 52, as described in section 9.1.

Primary Efficacy Analysis for the Combined 2Q8 and 2Q16 Groups at Week 24

This analysis will be conducted on the FAS and will include the primary efficacy endpoint at week 24 for the combined 2Q8 and 2Q16 groups only.

Primary Efficacy Analysis for the 2Q8 and 2Q16 Groups at Week 52

This analysis will be conducted on the FAS and will include the primary efficacy endpoint at week 52 for the 2Q8 and 2Q16 groups separately.

9.5.2.1. Analyses of Primary and Secondary Efficacy Variables

Primary Efficacy Variable

The primary efficacy variable analysis will be conducted on the FAS population. The primary analysis is a statistical evaluation of superiority of 3 comparisons (combined aflibercept vs. sham at week 24, aflibercept 2Q8 vs. sham at week 52, and aflibercept 2Q16 vs. sham at week 52) in respect to the primary efficacy variable (see section 8.2). The statistical analysis will be performed using the Cochran-Mantel-Haenszel method, stratified by baseline DRSS level (level 47 vs. level 53). Missing or nongradable post-baseline values will be imputed using the LOCF procedure. For any patient who receives rescue treatment, the measurements after rescue is given will be imputed using the last observation prior to rescue treatment. Baseline values will be carried forward if all post-baseline observations are missing or nongradable.

Aflibercept treatment will be considered to be superior to sham if the estimated aflibercept group (combined, aflibercept 2Q8, or aflibercept 2Q16) is greater than the sham group, and the p-value is less than or equal to or statistically significant at a 1.67% level.

As stated above, for the primary efficacy analysis, any patient who receives rescue treatment in the study eye will have all efficacy measurements collected after rescue treatment is imputed using the last observation prior to such treatment. For a sensitivity analysis, the primary efficacy analysis will also be performed using all observed measurements (regardless of whether rescue treatment was given), and only true missing values will be imputed using the LOCF procedure. Baseline values will be carried forward if all post-baseline observations are missing or nongradable.

Secondary Efficacy Variables

If at least one of the aflibercept groups is shown to be superior to sham in the primary variable, additional comparisons will be made for this aflibercept group with respect to the secondary variables at week 52, using the significance level specified in section 9.1.

A hierarchical testing procedure will be performed for each dose group to compare the secondary variables between the respective aflibercept group and sham in the following order:

- 2Q8 secondary endpoints at week 52
  - Proportion of patients developing a vision-threatening complication due to diabetic retinopathy
  - Proportion of patients who develop CI-DME
  - Time to development of a vision-threatening complication
  - Time to development of CI-DME
  - Proportion of patients who receive PRP, inclusive of patients undergoing vitrectomy with endolaser
  - AUC for change in BCVA from baseline
- 2Q16 secondary endpoints at week 52
  - Proportion of patients developing a vision-threatening complication due to diabetic retinopathy
  - Proportion of patients who develop CI-DME
  - Time to development of a vision-threatening complication
  - Time to development of CI-DME
  - Proportion of patients who receive PRP, inclusive of patients undergoing vitrectomy with endolaser
  - AUC for change in BCVA from baseline

The p-values at week 52 for the secondary endpoints will be reported for all comparisons between the aflibercept groups and the sham group; however, a superiority claim can be made for a given endpoint only if all preceding endpoint comparisons in the hierarchy are shown to be statistically significant at a significance level specified in section 9.1. The hierarchical method ensures the overall type I error rate of 5% for this study, with multiplicity adjustment for primary and secondary endpoint analyses.

All endpoints will also be analyzed descriptively at week 100 in an exploratory manner.

The analysis of proportion variables will be done using the same methodology as for the analyses of the primary efficacy variable described in this section.

For continuous variables (ie, BCVA), an analysis of covariance (ANCOVA) model with baseline measurements of the continuous variable as covariates and treatment and baseline DRSS score (level 47 vs. level 53) stratification as fixed factors will be used for the endpoint. The pair-wise comparisons of each aflibercept group versus sham will be done in the ANCOVA model. In addition, 2-sided 95% confidence intervals for the difference of each aflibercept group minus sham will be calculated.

Time to first vision-threatening complication (composite of PDR [inclusive of patients who have vitreous hemorrhage or tractional retinal detachment believed to be due to PDR] and ASNV) will be analyzed using the Kaplan-Meier estimates. A log-rank test will be performed, comparing sham with the aflibercept groups, as well as 2-sided 95% confidence intervals for the time to first vision-threatening complication for the difference of each comparison group. Time to development of CI-DME will be analyzed similarly.

Similar to the analysis of the primary endpoint, any patient who receives rescue treatment in the study eye will have all efficacy measurements collected after rescue treatment imputed using the last observation prior to such treatment. For a sensitivity analysis, the primary efficacy analysis will also be performed using all observed measurements (regardless of whether rescue treatment was given) and only true missing values will be imputed using the LOCF procedure. Baseline values will be carried forward if all post-baseline observations are missing.

Analyses of the primary and secondary endpoints may also be performed on subsets of the FAS, such as patients who have developed CI-DME, PDR, or patients who have had a vitrectomy. Such subsets will be defined in the SAP.

9.5.2.2. Analyses of Additional Efficacy Variables

All additional efficacy variables (see section 8.3) will be analyzed descriptively. In addition, the primary and secondary variables will be also analyzed descriptively at week 100. These descriptive analyses may include statistical tests on the proportion for the efficacy variables, in the same way as described for the primary and secondary efficacy variable analyses (see section 9.5.2.1).

The analysis of categorical variables will be done using the same methodology used for the analysis of the primary efficacy variable described in section 9.5.2.1. Analyses of continuous variables (eg, central retinal thickness, median deviation on visual field) will use a 2-way ANCOVA main effects models with treatment group and baseline DRSS (level 47 vs. level 53) stratification as fixed factors and baseline assessment of the efficacy outcome measure as a

covariate. The pairwise comparisons of each aflibercept treatment group versus sham will be done in these models by corresponding CONTRAST statements and a point-estimate. A 2-sided 95% confidence interval for the treatment difference of each aflibercept treatment group minus sham will be calculated.

9.5.3. Safety Analysis

Safety variables will be summarized on the SAF through week 24 for the combined 2Q8 and 2Q16 group, and the sham group. Safety data accumulated through week 52 and week 100 for each treatment group will be summarized at the respective time point.

9.5.3.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- 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

A TEAE is defined as an event (or an exacerbation of a preexisting event during the treatment period) that is observed or reported after the first administration of study drug, and no later than 30 days after last administration of study drug (active or sham injection).

Analysis

All AEs reported in this study will be coded using the currently available version of the MedDRA. Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group, and by ocular study eye, ocular fellow eye, and non-ocular TEAEs, will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in section 7.3.1), presented by SOC and PT
- TEAEs by relationship to drug or injection procedures (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

9.5.3.2. Ocular Safety

Ocular safety variables (eg, IOP measurements) will be analyzed descriptively at their scheduled visit, including changes from baseline. All ocular safety parameters will be summarized using descriptive statistics. Information from OCT, FP, and FA may also be used to assess ocular safety.

9.5.3.3. Other Safety

Vital Signs

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

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

9.5.3.4. Treatment Exposure

Exposure to study drug will be examined for each patient. The total number of treatments administered to each patient and the duration of treatment will be analyzed and summarized using descriptive statistics by treatment group in the SAF and FAS populations.

9.5.3.5. Treatment Compliance

Compliance with protocol-defined study medication will be calculated as follows:

Treatment compliance = (number of received injections [active or sham] through a given week)/(number of planned injections [active or sham] during the period of participation in the study through the given week) x 100%.

The 24-week treatment period is defined as the period from day 1 to week 16 (visit 6; last study treatment visit) plus 28 days. For all treatment groups, the 52-week treatment period is defined as the period from day 1 to week 48 (visit 10/last study treatment visit), and the 100-week treatment period is defined as the period from day 1 to week 96 (visit 17/last study treatment visit) plus 28 days. Sham injections will be counted as planned treatment.

9.6. Interim Analysis

No formal interim analysis is planned.

9.7. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The baseline assessment is defined as the latest valid pre-dose assessment

General rules for handling missing data:

- Rules for handling missing data for efficacy assessments will use LOCF for patients in analysis populations as described. Additional details will be provided in the SAP.
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the CRF assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with nonprotocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

9.8. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

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 Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, 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 an electronic data capture (EDC) tool, Medidata RAVE.

10.2. Electronic Systems

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

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- SAS – statistical review and analysis
- Argus – a pharmacovigilance and clinical safety software system

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with ICH guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient 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 sponsor upon request.

11.2. Source Document Requirements

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

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs by trained site personnel. A CRF must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

12. AUDITS AND INSPECTIONS

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

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor'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 sponsor immediately
- Taking all appropriate measures requested by the sponsor 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 sponsor 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.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor 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 GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB. A copy of the IRB-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

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

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

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

13.3. Patient Confidentiality and Data Protection

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

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

13.4. 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 patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB 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 patients 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 the sponsor 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.

14. PROTOCOL AMENDMENTS

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

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

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

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

16.2. 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 15 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 sponsor 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 sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

Antithrombotic Trialists' Collaboration. Collaborative overview of randomized trial of antiplatelet therapy – II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. Br Med J 1994; 308:168-171.

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 3, Double-Masked, Randomized Study of the Efficacy and Safety of Intravitreal Aflibercept Injection in Patients with Moderately Severe to Severe Nonproliferative Diabetic Retinopathy, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Conference on Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. OPTICAL COHERENCE TOMOGRAPHY - ANGIOGRAPHY SUB-STUDY

This is an exploratory study for OCT-angiography conducted as a sub-study to protocol VGFTe-OD-1411. Investigational sites that are participating in VGFTe-OD-1411 may choose to participate in this optional, exploratory OCT-angiography sub-study. In order to participate, sites must have the Optovue Angio-vue system installed.

A. OCT-Angiography Sub-study Objective

The objective of this sub-study is to explore the use of OCT-angiography to monitor vascular leak and other disease characteristics in patients with diabetic retinopathy treated with aflibercept versus sham. Since OCT-angiography has the ability to image vessels based on fluid flow characteristics, and more accurately, delineate the vascular layers, it may provide additional information related to treatment response beyond that achievable with standard OCT imaging.

B. Number of Patients and Sites

Patients will be enrolled at the investigator's discretion at sites that have access to the Optovue Angio-vue system. There will be no cap on the number of patients or sites that may participate.

C. Timing of OCT-Angiography

Optical coherence tomography-angiography will be performed approximately quarterly at the time points indicated in Table 1 and Table 2, in conjunction with the scheduled study visits for the main study.

Table 1: Schedule of Events (OCT-Angiography) – Year 1

Study Procedure	Screening Visit 1	Year 1 Treatment Period			
		Visit 5	Visit 7	Visit 9	Visit 11
Week	--	12	24	40	52
Day (visit window)	-21 to -1	85 ± 7 days	169 ± 7 days	281 ± 7 days	365 ± 10 days
Signed Informed Consent	X				
Optical Coherence Tomography - Angiography	X	X	X	X	X

Table 2: Schedule of Events (OCT-Angiography) – Year 2

Study Procedure	Visit 13	Visit 15	Visit 18/End of Study
Week	64	80	100
Day (visit window)	449 ± 7 days	561 ± 7 days	701 ± 10 days
Optical Coherence Tomography - Angiography	X	X	X

Detailed instructions for image collection and transmission will be provided in the study procedure manual.

APPENDIX 2. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG OR INJECTION PROCEDURE

Is there a reasonable possibility that the event may have been caused by the study drug or injection procedure?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug or injection procedure
- do not reappear or worsen when dosing with study drug or injection procedure is resumed
- are not a known response to the study drug or injection procedure based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug or injection procedure
- resolve or improve after discontinuation of study drug or injection procedure
- reappear or worsen when dosing with study drug or injection procedure is resumed
- are known to be a response to the study drug or injection procedure based upon preclinical data or prior clinical data

NOTE: This list is not exhaustive.

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Scientific/Medical Monitor, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the conduct of the study and the data generated.

Study Title: A Phase 3, Double-Masked, Randomized Study of the Efficacy and Safety of Intravitreal Aflibercept Injection in Patients with Moderately Severe to Severe Nonproliferative Diabetic Retinopathy

Protocol Number: VGFTe-OD-1411

Protocol Version: VGFTe-OD-1411 Amendment 5

See appended electronic signature page
Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page
Sponsor's Responsible Regulatory Representative

See appended electronic signature page
Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page
Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00052211 v1.0

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