Clinical Study Protocol

A RANDOMIZED, DOUBLE-MASKED, ACTIVE-CONTROLLED PHASE 2 STUDY OF THE EFFICACY, SAFETY, AND TOLERABILITY OF REPEATED DOSES OF INTRAVITREAL REGN910-3 IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Compound:	REGN910-3
Study Name:	ONYX
Clinical Phase:	2
Protocol Number:	R910-3-AMD-1517
Protocol Version:	R910-3-AMD-1517.03
Amendment 3 Date of Issue:	See appended electronic signature page
Amendment 2 Date of Issue:	01 May 2017
Amendment 1 Date of Issue:	16 June 2016
Original Date of Issue:	19 January 2016
Scientific/Medical Monitor:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

Amendment 3

The following table outlines the change made to the protocol and the affected section:

Change	Section
Corrected a change to exclusion criterion #22 regarding contraception that was mistakenly included as part of amendment 2. This exclusion criterion remains unchanged from the original protocol version dated 19 January 2016.	Section 4.2.2 Exclusion Criteria, exclusion criterion #22

Amendment 2

Purpose:

The purpose of this amendment is as follows:

1.) To update the primary endpoint to include timepoints through week 36, and to clarify the statistical analysis

2.) To update the requirements for measurement of blood pressure

3.) To update the safety section in regards to relationship to injection procedure and reporting of pregnancy outcomes, and to update the contraception language to conform to the current protocol template

Amendment 1 (16 June 2016)

Purpose:

The purpose of this amendment is as follows:

- To change the number of study sites from approximately 80 to approximately 95
- To add a standard exclusion criterion for sub-retinal hemorrhage in the study eye that was mistakenly omitted
- To allow additional treatment with intravitreal aflibercept injection (IAI) at non-active treatment visits, according to the investigator's discretion, intended to facilitate retention of patients in the study.
- To prohibit the use of bevacizumab in the fellow eye, to avoid potential confounding effects on interpretation of safety data
- To update the OCT-A appendix to include the Zeiss system, and to update the parameters of interest
- To correct the definition for PK analysis set
- To correct the definitions for ADA analysis set, ADA variables, and remove the discussion of ADA persistence in studies less than 1 year in length
- Editorial changes and corrections, including correction to table number in Appendix 1

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Double-Masked, Active-Controlled Phase 2 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal REGN910-3 in Patients with Neovascular Age-Related Macular Degeneration
Site Location(s) **Principal Investigator**	Approximately 95 sites in both the United States (US) and potentially outside of the US
Objective(s)	The primary objective of the study is to compare the efficacy of intravitreal (IVT)-administered REGN910-3 compared to intravitreal aflibercept injection (IAI) in improving best-corrected visual acuity (BCVA) in patients with age-related macular degeneration (AMD) The secondary objectives of the study are to assess: • If REGN910-3 demonstrates an anatomic benefit compared to IAI alone • The duration of effect of REGN910-3 following 3 initial monthly injections • The safety and tolerability of REGN910-3 • The presence of anti-REGN910 and anti-aflibercept antibodies in serum
Study Design	This is a phase 2, double-masked, active-controlled study of the efficacy, safety, and tolerability of repeated doses of IVT REGN910-3 versus IAI alone in patients with neovascular AMD. The study consists of a screening/baseline period, a treatment period, and an end of study/early termination visit. Eligible patients will be initially randomized in a 1:2:3 ratio to receive 3mg:2mg, [low-dose]) REGN910-3, 6 mg:2mg [high-dose]) REGN910-3, or 2 mg IAI alone for 3 initial doses. At week 12, patients will be re-randomized (stratified based on change from baseline to week 12 in BCVA) and dosed from week 16 through week 32. Patients will be evaluated at all study visits for ocular and systemic safety and efficacy and will be followed to week 36.
Study Duration	The duration of the study for a patient is approximately 36 weeks, excluding the screening period.

Sample Size:	The expected total number of patients is 360
Target Population:	The target study population is men and women 50 years and older with neovascular AMD.

Treatment(s)

Study Drug	REGN910-3 (REGN910 and IAI):
Dose/Route/Schedule:	Group 1 (low-dose): REGN910-3 (3 mg:2 mg) every 4 weeks (Q4) (day 1, week 4, and week 8) for 3 initial doses.
	Group 2 (high-dose): REGN910-3 (6 mg:2 mg) Q4 (day 1, week 4, and week 8) for 3 initial doses.
	Group 3 (IAI alone): IAI 2 mg Q4 (day 1, week 4, and week 8) for 3 initial doses
	At week 12, patients will be re-randomized (stratified based on change from baseline to week 12 in BCVA) into the following 3 treatment groups and dosed from week 16 through week 32 as follows:
	Group 1 (low-dose): REGN910-3 (3 mg:2 mg) Q8 with a sham injection administered at non-treatment visits
	Group 2 (high-dose): REGN910-3 (6 mg:2 mg)
	• Group 2a: REGN910-3 high-dose (6 mg:2 mg) at week 16 and Q8 through week 32, with sham injections at non-treatment visits
	• Group 2b: REGN910-3 high-dose (6 mg:2 mg) at week 20 and Q12 through week 32, with sham injections at non-treatment visits
	Group 3 (IAI alone):
	• Group 3a: IAI– 2 mg at week 16 and Q8 through week 32, with sham injections at non-treatment visits
	• Group 3b: IAI 2 mg at week 20 and Q12 through week 32, with sham injections at non-treatment visits
	• Group 3c: REGN910-3 high-dose (6 mg:2 mg) at week 16 and Q8 through week 32, with sham injections at non-treatment visits

Endpoint(s)	
Primary:	The primary endpoint in the study is the change from baseline in BCVA measured by the ETDRS letter score at week 12 through week 36
Secondary:	The secondary endpoints are: • Change from baseline in central subfield retinal thickness (CST) at week 12 through week 36 as measured by SD-OCT • Change in choroidal neovascularization (CNV) area from baseline (measured by FA) at week 12 through week 36 • Change in total lesion area from baseline (measured by FA) at week 12 through week 36
Procedures and Assessments	Visual function of the study eye and the fellow eye will be assessed using the 4-meter ETDRS protocol. The anatomical state of the retinal vasculature of the study eye and the fellow eye will be evaluated by funduscopic examination, FA, and FP. Anatomic characteristics of the retina will also be evaluated using autofluorescence. Retinal characteristics will be evaluated using SD-OCT (using a Heidelberg Spectralis, when possible). Overall safety will be assessed by monitoring/evaluating treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms (ECGs), and clinical safety laboratory testing. The potential emergence of anti-drug antibodies (ADAs) to REGN910 and aflibercept will also be evaluated. Ocular safety will be assessed by ophthalmic examinations (intraocular pressure [IOP], slit lamp examination, and indirect ophthalmoscopy). Pharmacokinetic and ADA assessments will be conducted. [redacted]
Statistical Plan	The sample size calculation is based on the change from baseline in BCVA by ETDRS letter score at week 12 in 2 comparisons: 3 mg:2 mg REGN910-3 (group 1) versus 2 mg IAI alone (group 3), and 6 mg:2 mg REGN910-3 (group 2) versus 2 mg IAI alone (group 3). The sample size was also determined based on the planned re-randomization of groups 2 and 3 at week 12. Assuming that the change in BCVA at week 12 compared to baseline is normally distributed, a true difference in the mean change of BCVA of 5 letters and an expected standard deviation (SD) of 11 letters for each group comparison of REGN910-3 and IAI, a sample size of 52 patients in group 1 (3 mg:2 mg REGN910-3) 104 patients in group 2 (6 mg: 2 mg REGN910-3), and 156 patients in group 3 (2 mg IAI alone) will be needed to provide at least 80% probability that the 95% confidence interval for the treatment difference will exclude 0. The assumption of the mean (SD) difference between groups 1 and 2 is based on the results from completed AMD studies (VIEW 1 and VIEW 2). A drop-out rate of approximately 15% was considered, resulting in 60, 120, and 180 patients for groups 1, 2, and 3,

respectively.

Analyses of all the efficacy variables at week 12 will be conducted using the full analysis set (FAS), and after week 12 using both the FAS and the "FAS Secondary Randomization" populations.

Efficacy analysis imputations will use the last observation carried forward (LOCF) procedure for patients in analysis populations. A sensitivity analysis on the primary efficacy endpoint will be performed to assess the effect of missing data.

The efficacy analysis for the primary efficacy endpoint will be the comparison between the REGN910-3 and IAI groups in the mean change in BCVA from baseline to week 12 through week 36. An analysis of covariance model with treatment as the main effect and baseline BCVA measurement as covariates will be employed to calculate the least squares mean and the 2-sided 95% confidence interval of the treatment difference. For patients receiving additional treatment, their assessments will be censored from the next visit after the first additional treatment. Missing values on or before the visit receiving additional treatment will be imputed using the LOCF procedure.

Additional comparisons will be made between the REGN910-3 and IAI groups with respect to the secondary efficacy variables (CST, CNV area, and total lesion area). The analysis of the secondary endpoints, will be performed using the same methodology as for the analysis of the primary efficacy endpoint. For the categorical efficacy variable, a 2-sided 95% confidence interval using normal approximation for the treatment difference will be provided.

The safety variables will be analyzed on the SAF for the treatment period from baseline/day 1 through the end of study (week 36). The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Data will not be imputed for the safety analysis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
ADA	Anti-drug antibody
AE	Adverse events
ALT	Alanine Aminotransferase
AMD	Age-related macular degeneration
Ang2	Angiopoietin 2
APTC	Anti-Platelet Trialists' Collaboration
ARGUS	Pharmacovigilance and clinical safety software system
AST	Aspartate Aminotransferase
ATE	Arterial thromboembolic event
BCVA	Best-corrected visual acuity
BUN	Blood urea nitrogen
CNV	Choroidal neovascularization
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CST	Central subfield retinal thickness
DME	Diabetic macular edema
DR	Diabetic retinopathy
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAF	Fundus autofluorescence
FAS	Full analysis set
FP	Fundus photography
GCP	Good Clinical Practice
HDL	High-density lipoprotein
IAI	Intravitreal aflibercept injection
ICF	Informed consent form
ICH	International Council on Harmonisation
IOP	Intraocular pressure

Abbreviation	Definition of Term
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system
IVT	Intravitreal
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
OCT	Optical coherence tomography
PCSV	Potentially clinically significant value
PT	Preferred term
Q4	Every 4 weeks
Q8	Every 8 weeks
Q12	Every 12 weeks
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	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
SOC	System organ class
TEAE	Treatment-emergent adverse event
UPCR	Urine protein:creatinine ratio
VEGF	Vascular endothelial growth factor
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in adults over 50, with an estimated 1.75 million patients in the United States (US) affected with the late stage, vision-threatening form, and another 7 million at high risk of developing advanced disease (The Eye Diseases Prevalence Research Group 2004). Reports indicate that 64% of white patients diagnosed with advanced disease have choroidal neovascularization (CNV), a form of the disease characterized by the presence of subretinal or subretinal pigment epithelial neovascularization, serous or hemorrhagic sensory retinal detachment, or subretinal pigment epithelial hemorrhage (Tomany 2004). Geographic atrophy, the second most prevalent form of advanced disease, manifests with areas of partial or complete depigmentation, atrophy, and loss of the retinal pigment epithelium (Tomany 2004). Although CNV affects 10% of the population with AMD, it accounts for 90% of the vision loss associated with AMD (AMD Alliance International). In Japan, the prevalence of late stage AMD in individuals over 55 years old is 0.89%, with approximately 690,000 patients affected with the advanced neovascular form (Oshima 2001). Although no clinical intervention is currently available to reduce progression to geographic atrophy, treatment regimens using anti-vascular endothelial growth factor (anti-VEGF) therapies have proven effective in reducing the near-term, CNV associated vision loss in patients.

Angiogenesis is a major feature of several pathological processes, including tumor growth, chronic inflammatory diseases, and ocular vascular diseases, including neovascular AMD (Folkman 1995, Kuhnert 2008, Andrae 2008). In ocular diseases characterized by aberrant angiogenesis, neovascularization can have catastrophic effects on vision, leading to edema, hemorrhage, and, ultimately, blindness (Ambati 2012). Although multiple stimuli such as platelet derived growth factor beta (PDGFβ), angiopoietin 2 (Ang2), and others are involved in the development of ocular neovascularization, vascular endothelial growth factor (VEGF)-A plays a major role in this process (Campochiaro 2013). Vascular endothelial growth factor is an endothelial cell specific mitogen and survival factor that also promotes endothelial cell migration, vessel formation and permeability, in particular ocular vascular pathologies including neovascular AMD.

Anti-vascular endothelial growth factor therapy is standard of care treatment for neovascular or "wet" AMD. The efficacy and safety of intravitreal aflibercept injection (IAI) in this patient population is well characterized. However, while approximately 95% of patients maintained their vision (defined as losing fewer than 15 letters from baseline) in the VIEW 1 and VIEW 2 studies in patients with AMD, only approximately 30% of patients achieved an improvement of 15 or more letters in best-corrected visual acuity (BCVA) at 1 year. Moreover, these visual outcomes were obtained with dosing every 8 weeks (Q8) after 3 initial monthly doses. There is still the possibility of improving treatment outcomes or attaining similar efficacy with a longer, more convenient, dosing interval.

In vivo studies demonstrate that REGN910, an anti-Ang2 antibody, has pharmacological activity in preclinical rodent and rabbit models of pathological angiogenesis in the eye, both as a single agent and in combination with an anti-VEGF. Like VEGF, Ang2 expression is upregulated by

hypoxia and exposure to elevated glucose levels, and ocular levels of both Ang2 and VEGF are elevated in the eyes of humans afflicted with wet AMD or ischemic retinopathies, including retinopathy of prematurity and diabetic retinopathy. In addition, a growing body of experimental evidence indicates that not only are VEGF and Ang2 co-regulated in these disease states, but that they may also act together to promote pathological neovascularization and vascular permeability (Shen 2014, Lip 2004, Oshima 2004a, Oshima 2004b, Peters 2007). These observations together indicate that not only would pharmacological inhibition of Ang2 be likely to provide therapeutic benefit in the treatment of AMD, but that combined inhibition of Ang2 and VEGF could produce a greater therapeutic effect.

In addition to improving visual outcomes, targeting both the VEGF and Ang-2 pathways in neovascular eye disease also has the possibility of providing a longer duration of action resulting in a longer treatment interval. In a preclinical model of retinal neovascularization and chronic vascular leak, treatment with both intravenous (IV) REGN910 (15 mg/kg, IV) or intravitreal (IVT) aflibercept (125µg/50µl, IVT) resulted in a suppression of vascular leak through week 10, compared to only week 3 with aflibercept alone. Treatment with REGN910 alone did not significantly affect vascular permeability over the time course of the study.

This phase 2 study will explore the efficacy and safety of REGN910-3, a co-formulation for IVT injection consisting of REGN910 (nesvacumab) and IAI, in patients with neovascular AMD compared to IAI alone.

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

1.2. Rationale

1.2.1. Rationale for Study Design

A growing body of experimental evidence indicates VEGF and Ang2 are co-regulated in neovascular and ischemic retinopathies and that they may act together to promote pathological neovascularization and vascular permeability (Lip 2004, Oshima 2004a, Oshima 2004b, Peters 2007). Further, preclinical in vivo studies demonstrate that REGN910 has pharmacological activity in rodent and rabbit models of pathological angiogenesis in the eye, both as a single agent and in combination with a VEGF blocker. In the phase 1 clinical study, the combination appeared to be tolerable. Collectively, these observations indicate that not only would pharmacological inhibition of Ang2 be likely to provide therapeutic benefit in the treatment of neovascular AMD, but that combined inhibition of Ang2 and VEGF could produce a greater therapeutic effect than inhibition of either angiogenic factor alone.

This phase 2 study will explore the efficacy and safety of REGN910-3, a co-formulation for IVT injection consisting of REGN910 and IAI in patients with neovascular AMD compared to IAI alone.

1.2.2. Rationale for Dose Selection

The phase 1, open-label, dose escalation study of IVT REGN910-3 (REGN910 and IAI) in patients with either neovascular AMD or diabetic macular edema (DME) (R910-3-OD-1403) evaluated doses of 0.5 mg:2 mg, 1 mg:2 mg, 3 mg:2 mg, and 6 mg:2 mg, and 6 mg REGN910 alone. The 2 highest doses in this study (REGN910-3 low-dose [3 mg:2 mg] and REGN910-3 high-dose [6 mg:2 mg]) were both well tolerated. The observed C_{max} values following IVT administration were approximately 85- to 160-fold lower than those observed following administration of the lowest IV dose (1 mg/kg) in oncology studies with systemic administration. Thus, the IVT doses in this study provide adequate margins with regard to safety.

The IAI monotherapy dose of 2 mg is in accordance with the dose that is currently approved in multiple countries, including the US and Japan, as EYLEA® for the treatment of neovascular AMD, DME, and macular edema following retinal vein occlusion (central retinal vein occlusion and branch retinal vein occlusion). In the US, EYLEA is also approved for the treatment of diabetic retinopathy in patients with DME. In Japan, EYLEA is also approved for the treatment of myopic choroidal neovascularization.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to compare the efficacy of IVT-administered REGN910-3 compared to IAI in improving BCVA in patients with AMD.

2.2. Secondary Objectives

The secondary objectives of the study are to assess:

- If REGN910-3 demonstrates an anatomic benefit compared to IAI alone
- The duration of effect of REGN910-3 following 3 initial monthly injections
- The safety and tolerability of REGN910-3
- The presence of anti-REGN910 and anti-aflibercept antibodies in serum

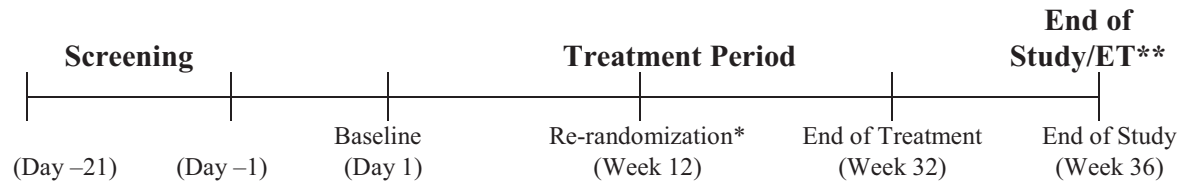
3. STUDY DESIGN

3.1. Study Description and Duration

This is a randomized, double-masked, active-controlled phase 2, multi-center study of the efficacy and safety of repeated doses of IVT REGN910-3 versus IAI alone in patients with neovascular AMD. Study visits will occur every 4 weeks (Q4) for a duration of 36 weeks. The primary endpoint will be assessed at week 12 through week 36. After providing informed consent, patients will be assessed for study eligibility at the screening visit, which may occur up to 3 weeks before day 1/baseline (visit 2). At day 1/baseline (visit 2), patients will undergo safety assessments prior to receiving the first dose of study drug.

The study consists of a screening/baseline period, a treatment period, and an end of study/early termination visit (see Figure 1).

Figure 1: Study Flow Diagram



*Patients in group 2 (REGN910-3 high-dose) and group 3 (IAI only)
**ET = Early Termination

Eligible patients will be randomized in a 1:2:3 ratio to receive low-dose (3 mg:2 mg) REGN910-3 (group 1), high-dose (6 mg:2 mg) REGN910-3 (group 2), or 2 mg IAI alone (group 3). The unequal randomization will allow for a re-randomization at week 12 of patients in groups 2 and 3 into subgroups for subsequent analysis at week 36.

On day 1, week 4, and week 8, patients in each treatment group will receive an injection of study drug for a total of 3 doses.

At week 12, patients in group 1 will continue to receive REGN910-3 (low-dose) Q8 beginning at week 16, with sham injections at non-treatment visits.

At week 12, patients in groups 2 and 3 will be re-randomized, and stratified by BCVA (using 5 strata reflecting change in BCVA [Early Treatment Diabetic Retinopathy Study (ETDRS) letters] from baseline to week 12: <0 letters, 0≤ BCVA <5 letters, 5≤ BCVA <10 letters, 10≤ BCVA <15 letters, and BCVA ≥15 letters) (Figure 2) as follows:

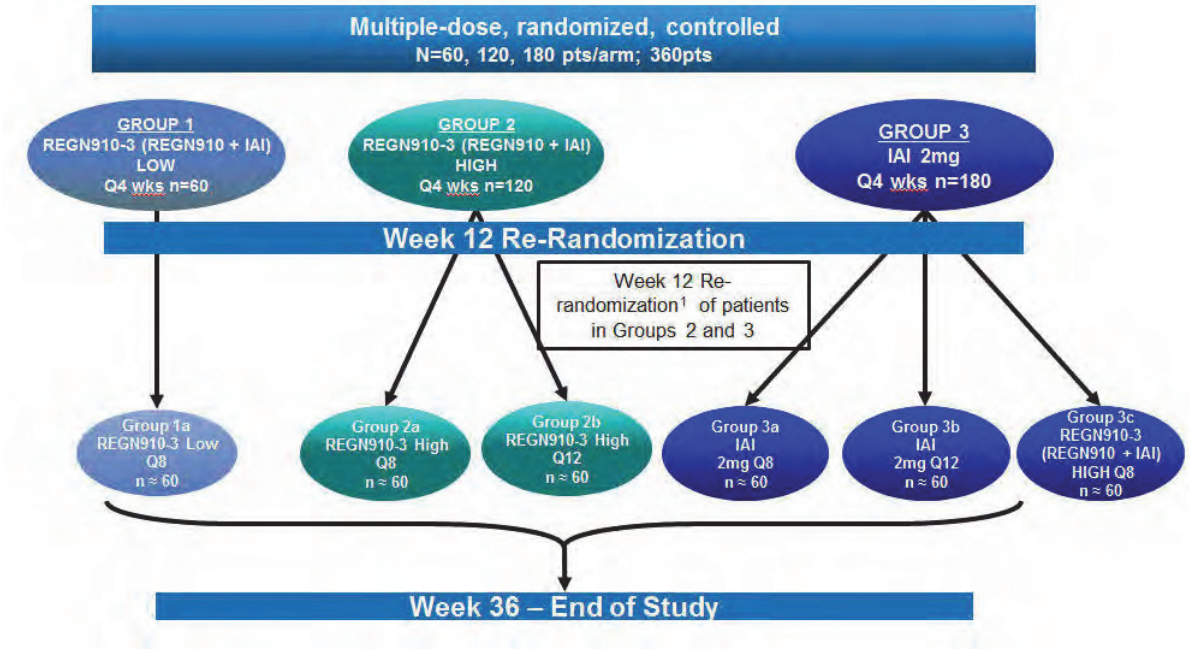
Patients in group 2 will be re-randomized into 2 groups, with dosing from week 16 through week 32 as indicated:

- Group 2a: REGN910-3 high dose (6 mg:2 mg) Q8 beginning at week 16, with sham injections at non-treatment visits
- Group 2b: REGN910-3 high dose (6 mg:2 mg) every 12 weeks (Q12) beginning at week 20, with sham injections at non-treatment visits

Patients in group 3 will be re-randomized into 3 groups, with dosing from week 16 through week 32 as indicated:

- Group 3a: IAI 2 mg Q8 beginning at week 16, with sham injections at non-treatment visits
- Group 3b: IAI 2 mg Q12 beginning at week 20, with sham injections at non-treatment visits
- Group 3c: REGN910-3 high-dose (6 mg:2 mg) Q8 beginning at week 16 with sham injections at non-treatment visits

Figure 2: Study Flow Figure



[1] Stratification for re-randomization will be based on VA outcomes at week 12

Patients will be evaluated at all study visits for ocular and systemic safety and efficacy (including BCVA using the 4-meter Early Treatment Diabetic Retinopathy Study [ETDRS] protocol, ophthalmic examinations, spectral domain optical coherence tomography [SD-OCT], fluorescein angiography [FA]/ fundus photography [FP], fundus autofluorescence (FAF), laboratory assessments, etc) and will be followed to week 36.

[redacted]

3.1.1. End of Study Definition

The end of study for this study is defined as the last visit of the last patient.

3.2. Planned Interim Analysis

No interim analysis is planned.

3.3. Study Committees

Potential arterial thromboembolic events will be evaluated by a masked adjudication committee according to criteria formerly applied and published by the Anti-Platelet Trialists' Collaboration (APTC) prior to database unmasking (Antithrombotic Trialists' Collaboration 1994; Antithrombotic Trialists' Collaboration 2002). An arterial thromboembolic event is defined as a nonfatal MI, 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 reference manual.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

A total of approximately 360 patients with AMD will be enrolled at approximately 95 sites in the US, which may include sites outside of the US.

4.2. Study Population

The study population will be men and women who are aged 50 years and older with neovascular AMD.

Patients must meet all eligibility criteria at screening and baseline (day 1) visits, however, need not repeat assessments that are only required at screening.

4.2.1. Inclusion Criteria

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

1. Men or women ≥50 years of age with active subfoveal CNV secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye as assessed by a central reading center
2. BCVA ETDRS letter score of 73 to 24 (Snellen equivalent of 20/40 to 20/320) in the study eye.
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 will be excluded from the study:

1. Evidence of CNV due to any cause other than AMD in either eye
2. Prior IVT anti-VEGF (IAI, ranibizumab, bevacizumab or pegaptanib sodium) in the study eye
3. Evidence of DME or diabetic retinopathy (defined as more than 1 microaneurysm) in either eye in diabetic patients
4. Any history of macular hole of stage 2 and above in the study eye
5. Only 1 functional eye, even if that eye was otherwise eligible for the study (eg, BCVA of counting fingers or less in the eye with worse vision)
6. Ocular conditions with poorer prognosis in the fellow eye
7. Any prior treatment with angiopoietin inhibitors
8. Any prior systemic (IV) anti-VEGF administration
9. History of vitreoretinal surgery in the study eye

10. Previous use of intraocular or periocular corticosteroids in the study eye within 4 months of screening
11. Intraocular pressure (IOP) ≥25 mm Hg in the study eye
12. Evidence of infectious blepharitis, keratitis, scl**e**ritis, or conjunctivitis in either eye at the time of screening/randomization
13. Any intraocular inflammation/infection in either eye within 3 months of the screening visit
14. Current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in the study eye
15. Inability to obtain photographs, FA or SD-OCT, eg, due to media opacity, allergy to fluorescein dye or lack of venous access
16. Uncontrolled diabetes mellitus in the opinion of the investigator
17. Uncontrolled blood pressure (defined as systolic >160 mm Hg or diastolic >95 mm Hg while patient is sitting)
18. History of cerebrovascular accident or myocardial infarction within 180 days of screening visit
19. Renal failure, dialysis, or history of renal transplant
20. Known sensitivity to any of the compounds of the study formulation
21. Pregnant or breast-feeding women
22. 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.
23. Sub-retinal hemorrhage in the study eye that is 50% or more of the total lesion area

* 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.

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, need for treatment in the study eye that is beyond what is designated in the protocol, 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 at the early termination visit, per section 6.1.

4.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

REGN910-3 is a drug product that is composed of REGN910 (anti-Ang2 antibody, INN: nesvacumab) and IAI. REGN910-3 will be supplied for this study as an aqueous solution in sterile, sealed, single-use vials for IVT administration in concentrations of 60:40 mg/mL, and 120:40 mg/mL, each with an injection volume of 50 µL (0.05 mL). There will be a 50 µL (0.05 mL) minimum withdrawable volume from the vial.

Intravitreal aflibercept injection will be supplied for this study as an aqueous solution in sterile, sealed, single-use vials for IVT administration at a concentration of 40 mg/mL and an injection volume of 50 µL (0.05 mL). There will be a 50 µL (0.05 mL) withdrawable volume from the vial.

Empty vials will be supplied for sham injection.

There will initially be 3 treatment groups that will receive 1 of the following parallel treatments as follows:

- Group 1 (low-dose): REGN910-3 (3 mg:2 mg) Q4 (day 1, week 4, and week 8) for 3 initial doses followed by Q8 dosing beginning at week 16. A sham injection will be administered at non-treatment visits
- Group 2 (high-dose): REGN910-3 (6 mg:2 mg) Q4 (day 1, week 4, and week 8) for 3 initial doses. At week 12, patients will be re-randomized (stratified based on change from baseline to week 12 in BCVA) into the following 2 treatment groups:
  - Group 2a: REGN910-3 high-dose (6 mg:2 mg) at week 16 and Q8 through week 32, with sham injections at non-treatment visits
  - Group 2b: REGN910-3 high-dose (6 mg:2 mg) at week 20 and Q12 through week 32, with sham injections at non-treatment visits

- Group 3 (IAI alone): IAI 2 mg Q4 (day 1, week 4, and week 8) for 3 initial doses

  At week 12, patients will be re-randomized (stratified based on change from baseline to week 12 in BCVA) into the following 3 treatment groups:

  - Group 3a: IAI– 2 mg at week 16 and Q8 through week 32, with sham injections at non-treatment visits
  - Group 3b: IAI 2 mg at week 20 and Q12 through week 32, with sham injections at non-treatment visits
  - Group 3c: REGN910-3 high-dose (6 mg:2 mg) at week 16 and Q8 through week 32, with sham injections at non-treatment visits

Instructions on dose preparation are provided in the pharmacy manual.

5.2. Additional Treatment

Although efforts should be made to ensure adherence to the protocol-specified dosing interval, beginning at week 12, if, in the investigator's judgement, the patient cannot adhere to the protocol-specified dosing interval due to persistent or worsening disease and requires an interim injection, the patient may receive additional treatment. The investigator must make reasonable efforts to consult with the study director or sponsor designee prior to the additional treatment being allowed. Patients will receive IAI 2 mg if it is determined that additional treatment will be administered.

Patients who qualify for additional treatment will continue to receive their randomized treatment at future visits. Patients will continue to be masked to treatment interval.

5.3. Dose Modification and Study Drug Discontinuation Rules

5.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

5.3.2. 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 end-of-study assessments, per section 6.1.

5.3.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of evidence of pregnancy.

5.3.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug dosing may be temporarily stopped as deemed necessary by the investigator. Treatment can be resumed if it is considered in the patient's best medical interest by the investigator.

5.4. Method of Treatment Assignment

Approximately 360 patients will be initially randomized in a 1:2:3 ratio to receive either 3 mg:2 mg REGN910-3, 6 mg:2 mg REGN910-3, or 2 mg IAI according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study staff (or qualified designee). The unequal randomization will allow for a re-randomization of patients in groups 2 and 3 at week 12 into subgroups for subsequent analysis at week 36 as described in section 3.1.

Patients re-randomized in groups 2 and 3 will be stratified based on change from baseline to week 12 in BCVA.

5.4.1. Masking

This is a double-masked study. During the first 8 weeks of the study, each patient will receive active injections at each visit. At week 12, neither active treatment nor sham injections will be administered. Study patients, the principal investigators, and study site personnel will be masked to all randomization assignments. The Regeneron Study Director, Medical Monitor, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain masked to all patient randomization assignments.

Starting at week 16, patients in groups 1, 2a, 3a, and 3c will receive active treatment Q8 with sham injections at non-treatment visits. Patients in groups 2b and 3b will receive a sham injection at week 16 and then active injections Q12 beginning at week 20 with sham injections at subsequent non-treatment visits. During this period, study drug or sham injections will be administered by an injecting physician. This individual, who will be masked to treatment assignment, should assess safety at approximately 30 minutes post IVT injection. The same injecting physician may also assess the need for re-treatment, additional treatment, AEs, and efficacy.

Every effort will be made to ensure that the visual acuity examiner remains masked to treatment assignment in order to allow for an unbiased assessment of visual acuity. The visual acuity examiner should only perform the assigned task of visual acuity assessments and should make every effort to remain masked to patient's previous letter score and study eye.

Masked study drug kits coded with a medication numbering system will be used. In order to maintain the mask, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

5.4.2. 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 treatment assignment will be performed using the IVRS; manual unmasking (ie, via the designated study pharmacist 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 for a serious adverse event (SAE) that is unexpected and for which a causal relationship to study drug cannot be ruled out, only the Regeneron Head of Pharmacovigilance and Risk Management, or designee, will unmask the patient.

5.5. Treatment Logistics and Accountability

5.5.1. Packaging, Labeling, and Storage

A medication numbering system will be used in labeling masked investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the mask, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site [redacted]; storage instructions will be provided in the pharmacy manual and clinical label.

5.5.2. Supply and Disposition of Treatments

Study drug will be shipped [redacted] to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be returned to the sponsor or designee.

5.5.3. 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.

5.5.4. Treatment Compliance

All study drugs will be administered by qualified site personnel (a trained ophthalmologist) in a research clinic. Compliance with study drug dosing will be monitored by review of clinic records. All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

5.6. Concomitant Medications

Any treatment administered from the first dose of study drug 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.

5.6.1. Prohibited Medications

Study Eye

Patients may not receive any standard or investigational agents for AMD treatment in the study eye other than their assigned study treatment with IVT REGN910-3 or IAI, as specified in this protocol. This includes medications administered locally (eg, IVT, topical, juxtascleral or periorbital routes), as well as those administered systemically, with the intent of treating neovascular AMD in the study eye or fellow eye.

Fellow Eye

Starting at week 4, if the fellow eye has neovascular AMD, IAI (2 mg) may be administered. Patients may not receive bevacizumab in the fellow eye.

Non-Ocular (Systemic)

Non-ocular (systemic) standard or investigational treatments for neovascular AMD of the study or fellow eye are not permitted. Systemic anti-angiogenic agents and anti-ang2 inhibitors will not be permitted during the study.

5.6.2. Permitted Medications

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 1.

Table 1: Schedule of Events

Study Procedure	Screening Visit 1	Baseline Visit 2	Treatment Period								EOS/ET
			Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Week	--	--	4	8	12	16	20	24	28	32	36
Day (visit window)	-21 to -1	1	28 ± 7 days	56 ± 7 days	84 ± 7 days	112 ± 7 days	140 ± 7 days	168 ±7 days	196 ±7 days	224 ±7 days	252 ±7 days
Screening/Baseline:											
Informed consent	X										
[redacted]	[redacted]										
Inclusion/exclusion	X	X									
Medical history	X										
Demographics	X										
Review of concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Treatment:											
Administer study drug or sham (all groups)[1]		X	X	X		X	X	X	X	X	
Efficacy:											
BCVA (ETDRS) and refraction	X	X	X	X	X	X	X	X	X	X	X
FA, FP, FAF	X				X			X			X
SD-OCT[2]	X	X	X	X	X	X	X	X	X	X	X
Safety:											
Ocular											
Intraocular pressure[3]	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
Indirect ophthalmoscopy[4]	X	X	X	X	X	X	X	X	X	X	X
Non-Ocular											
Physical examination	X										
Vital signs [5]	X	X	X	X	X	X	X	X	X	X	X
Height & body weight	X										
ECG	X										X
Adverse events [6]	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Screening Visit 1	Baseline Visit 2	Treatment Period								EOS/ET
			Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Week	--	--	4	8	12	16	20	24	28	32	36
Day (visit window)	-21 to -1	1	28 ± 7 days	56 ± 7 days	84 ± 7 days	112 ± 7 days	140 ± 7 days	168 ±7 days	196 ±7 days	224 ±7 days	252 ±7 days
Laboratory Testing:[7]											
Hematology & blood chemistry	X				X						X
Urinalysis/UPCR	X				X						X
Pregnancy Test, women of childbearing potential[8]	serum	urine	urine	urine		urine	urine	urine	urine	urine	
REGN910 and aflibercept PK samples [9]		X	X	X	X	X	X	X	X	X	
Anti-REGN910 and anti-aflibercept antibody samples [9]		X					X				X
[redacted]		[redacted]									

*Sham injection to be administered

ECG = electrocardiogram, FA = fluorescein angiography, FP = fundus photography, FAF = fundus autofluorescence, SD-OCT = spectral domain optical coherence tomography, UPCR = Urine Protein Ratio, ET = early termination

1. Refer to pharmacy manual for study drug and sham injection protocol. Following study drug/sham injection, patients will be observed for approximately 30 minutes after administration of study drug.
2. When possible, SD-OCT should be performed on a Heidelberg Spectralis, and the same imaging system used at screening and day 1 must be used at all follow-up visits.
3. Intraocular pressure should be measured at all study visits (bilateral). On days when study drug is administered, it should be measured pre-dose (bilateral) and approximately 30 minutes after administration of study drug (study eye only).
4. Indirect ophthalmoscopy should be performed at all study visits (bilateral). On days when study drug is administered, it should be performed pre-dose (bilateral) and immediately after administration of study drug (study eye only).
5. Vital signs (body temperature, blood pressure, and heart rate) should be measured after the patient has been sitting for 5 minutes.
6. If a patient withdraws from the study, ongoing AEs should be followed to the end of study visit or until the patient withdraws consent.
7. All samples collected for laboratory assessments should be obtained prior to administration of study drug.
8. For women of childbearing potential, a negative serum pregnancy test at screening is required for eligibility. 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.
9. Pharmacokinetic samples (serum for REGN910 and plasma for aflibercept) should be drawn pre-dose on all visits through week 32. All ADA serum samples should be collected prior to administration of study drug.

[redacted]

6.1.1. Early Termination Visit

Patients who are withdrawn before the end of the study will be asked to return to the clinic to complete the visit 11 (EOS) assessments, as listed in Table 1.

6.1.2. Unscheduled Visits

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

6.2. Study Procedures

6.2.1. Procedures Performed only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: inclusion/exclusion criteria, medical history, demographics, physical examination, measurements of height and body weight, serum pregnancy test, and presentation of the informed consents for the main study [redacted].

6.2.2. Efficacy Procedures

6.2.2.1. Best Corrected Visual Acuity

Visual function of the study eye and the fellow eye will be assessed using the 4M ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group 1985) at each study visit, according to section 6.1. Visual acuity examiners must be certified to ensure consistent measurement of BCVA, and the examiner should make every effort to remain masked to the patient's previous letter scores and to study eye. A detailed protocol for conducting visual acuity testing and refraction can be found in the study reference manual.

6.2.2.2. Fluorescein Angiography/Fundus Photography

The anatomical state of the retinal vasculature of the study eye and the fellow eye will be evaluated by funduscopic examination, FA, and FP at time points according to section 6.1.

Certified photographers will perform FA and FP in both eyes at time points listed in section 6.1. Fundus and angiographic images will be sent to the independent reading center. The study eye will be the transit eye. All FA and FP will be archived at the site as part of the source documentation.

Photographers will be certified by the reading center to ensure consistency and quality in image acquisition. A detailed protocol for image acquisition and transmission can be found in the study reference manual.

6.2.2.3. Fundus Autofluorescence

Anatomic characteristics of the retina will also be evaluated using autofluorescence. Certified photographers will perform FAF at time points listed in section 6.1. Images will be sent to the

independent reading center. All images will be archived at the site as part of the source documentation.

Photographers will be certified by the reading center to ensure consistency and quality in image acquisition. A detailed protocol for image acquisition and transmission can be found in the study reference manual.

6.2.2.4. Spectral Domain Optical Coherence Tomography

Retinal characteristics will be evaluated using SD-OCT (using a Heidelberg Spectralis, when possible) at time points according to section 6.1. The same SD-OCT machine must be used for each patient throughout the study.

Images will be captured and transmitted at the study site by OCT technicians using SD-OCT for the study eye and fellow eye. Optical coherence tomography images will be sent to the independent reading center where images for the study eye will be read. All SD-OCTs will be electronically archived at the study sites as part of the source documentation. Optical coherence tomography technicians will be certified by the reading center to ensure consistency and quality in image acquisition. A detailed protocol for acceptable OCT machines and SD-OCT image acquisition/transmission can be found in the study reference manual.

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

6.2.3. Safety Procedures

6.2.3.1. Vital Signs

Vital signs (temperature, blood pressure, and heart rate) after the patient has been sitting for 5 minutes will be collected at time points according to section 6.1.

6.2.3.2. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at time points according to section 6.1 and sent to a central reading center for interpretation. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT intervals will be recorded. The ECG strips or reports will be retained with the source.

6.2.3.3. Laboratory Testing

Hematology, blood chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites and can also be found in the study reference manual.

Samples for laboratory testing will be collected prior to administration of study drug, at time points according to section 6.1. Tests will include:

Blood Chemistry

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

*(low-density lipoprotein [LDL] and high-density lipoprotein [HDL])

Hematology

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

Urinalysis

Urine Protein:Creatinine Ratio (UPCR)	Glucose	RBC
Color	Blood	Hyaline and other casts
Clarity	Bilirubin	Bacteria
pH	Leukocyte esterase	Epithelial cells
Specific gravity	Nitrite	Crystals
Ketones	WBC	Yeast
Protein		

Other Laboratory Tests

All women of childbearing potential will have a serum pregnancy test during screening (a negative result is required for study eligibility) and a urine pregnancy test at baseline/treatment day 1. A negative urine pregnancy test is required before treatment is administered. Women of childbearing potential should continue to be tested for pregnancy (urine pregnancy test) during the study at every study visit at which treatment is administered (see section 6.1).

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the 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 investigator.

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

6.2.3.4. Intraocular Pressure

Intraocular pressure of both the study eye and fellow eye will be measured at time points according to section 6.1 using Goldman applanation tonometry or Tono-pen™. Intraocular pressure will be performed bilaterally pre-dose, and in the study eye post-dose on days of dosing. The post-dose measurement should be done approximately 30 minutes after administration of study drug (study eye only). If the IOP is elevated, it should be monitored until it normalizes. The same method of IOP measurement must be used in each patient throughout the study.

6.2.3.5. Slit Lamp Examination

The anterior eye structure and the ocular adnexa will be examined using a slit lamp at time points according to section 6.1.

6.2.3.6. Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed at time points according to section 6.1; patients' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre-dose (bilateral) and post-dose (study eye) by the investigator. Post-dose evaluation must be performed immediately after injection (active drug or sham).

6.2.4. Pharmacokinetic and Antibody Procedures

6.2.4.1. Drug Concentration Measurements and Samples

Samples (serum for REGN910, and plasma for aflibercept) for drug concentration will be collected pre-dose at time points listed in section 6.1.

[redacted]

6.2.4.2. Anti-drug Antibody Measurements and Samples

Serum samples for ADA assessment will be collected pre-dose at time points listed in section 6.1.

[redacted]

[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 pre-existing 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:
  - 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 reference 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 reference 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)/Ethics Committee (EC) 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/EC, 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 that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Refer to the study reference 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 reference 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
- All grade 3 or higher lab abnormalities

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 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 the injection procedure will be assessed by the 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 adverse event 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 Endpoints

The primary endpoint in the study is the change from baseline in BCVA measured by the ETDRS letter score at week 12 through week 36.

The secondary endpoints are:

- Change from baseline in central subfield retinal thickness (CST) at week 12 through week 36 as measured by SD-OCT
- Change in CNV area from baseline (measured by FA) at week 12 through week 36
- Change in total lesion area from baseline (measured by FA) at week 12 through week 36

8.2.1. Additional Efficacy Endpoints

The additional efficacy endpoints are:

- Proportion of patients with no retinal and/or subretinal fluid at week 12 through week 36
- Time to no retinal and/or subretinal fluid

A more comprehensive list of additional endpoints is captured in the statistical analysis plan.

8.3. Pharmacokinetic Variables

Concentrations of REGN910 in serum and concentrations of free aflibercept, and adjusted bound aflibercept in plasma will be summarized over time, and at each visit through week 36.

8.4. Anti-Drug Antibody Variables

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Total number of patients whose response in the ADA assay is negative at all timepoints analyzed
- Pre-existing immunoreactivity – defined either as a baseline positive ADA assay response (pre-dose at visit 1 or 2) with all post-dose ADA assay results negative, or a baseline positive assay response with all post-dose ADA assay responses less than 4-fold over baseline titer levels
- Treatment-emergent positive ADA response - defined as any post-dose positive ADA assay response when there is no baseline positive ADA response
- Treatment-boosted positive ADA response - defined as any post-dose positive ADA response that is at least 4-fold over baseline titer levels when baseline results are positive
- Titer values
- Titer category
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

9. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in section 8.

9.1. Statistical Hypothesis

Formal hypothesis testing will not be performed.

9.2. Justification of Sample Size

The sample size calculation is based on the change from baseline in BCVA by ETDRS letter score at week 12 in 2 comparisons: 3 mg:2 mg REGN910-3 (group 1) versus 2 mg IAI alone (group 3), and 6 mg:2 mg REGN910-3 (group 2) versus 2 mg IAI alone (group 3). The sample size was also determined based on the planned re-randomization of groups 2 and 3 at week 12.

Assuming that the change in BCVA at week 12 compared to baseline is normally distributed, a true difference in the mean change of BCVA of 5 letters and an expected standard deviation (SD) of 11 letters for each group comparison of REGN910-3 and IAI, a sample size of 52 patients in group 1 (3 mg:2 mg REGN910-3), 104 patients in group 2 (6 mg: 2 mg REGN910-3), and 156 patients in group 3 (2 mg IAI alone) will be needed to provide at least 80% probability that the 95% confidence interval for the treatment difference will exclude 0. The assumption of the mean (SD) difference between groups 1 and 2 is based on the results from completed AMD studies (VIEW 1 and VIEW 2). A drop-out rate of approximately 15% was considered, resulting in 60, 120, and 180 patients for groups 1, 2, and 3, respectively.

The sample size calculation was computed using the 2-group Satterthwaite (Moser 1989) t-test of unequal sample size of ratio at 1:2:3 by clinical assumption with equal variances using the commercial software nQuery Advisor 7.0.

9.3. Analysis Sets

9.3.1. Efficacy Analysis Sets

Full Analysis Set: The full analysis set (FAS) will include all randomized patients who received any study treatment, have a baseline measurement of BCVA, and at least 1 post-baseline assessment of BCVA.

The FAS will be used to evaluate all efficacy variables at week 12 through week 36. The analysis on the FAS will be performed according to the treatment assigned at baseline (as randomized). The week 36 analysis will be peformed according to the treatment assigned (as randomized) at week 12 for group 2 (REGN910-3 high-dose) and group 3 (IAI alone), or at baseline for group 1 (REGN910-3 low dose). Patients who are not re-randomized will be analyzed by their treatment group assigned at baseline.

FAS Secondary Randomization Set: This set will include all patients in the FAS who had completed the study through week 12, had received any study treatment after re-randomization (for patients in group 2 [REGN910-3 high-dose] and group 3 [IAI alone]), or after week 12 (for patients in group 1 [REGN910-3 low-dose]), and had at least 1 post-week 12 assessment of BCVA. The analysis on the "FAS Secondary Randomization" will be performed according to the treatment assigned (as randomized) at week 12 for group 2 (REGN910-3 high-dose), and group 3 (IAI alone), or at baseline for group 1 (REGN910-3 low-dose).

For efficacy analyses at week 36, the "FAS Secondary Randomization Set" will also be used.

9.3.2. Safety Analysis Set

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

9.3.3. Pharmacokinetic Analysis Set

The pharmacokinetic (PK) population includes all treated patients who received any study drug and who had at least 1 non-missing result for drug concentration following the first dose of study drug.

9.3.4. Anti-drug Antibody Analysis Set

The ADA population will include all treated patients who received any study drug and who had a reportable result for ADA following the first dose of study drug. The ADA analysis will be based on all treatments actually received (as treated).

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 at the re-randomization at week 12 for group 2 and group 3
- The total number of patients in each analysis set (eg, FAS, provided in section 9.3)
- The total number of patients who discontinued the study before weeks 12 and 36, with reasons for discontinuation
- A listing of patients treated but not randomized, and patients randomized but not treated, based on both the initial randomization and the re-randomization at week 12
- A listing of patients who discontinued from the study, along with reasons for discontinuation
- A listing of patients who received additional treatment in the study eye, including the total number of additional treatments and the visits at which they receivd additional treatment
- A listing of major protocol deviations

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, SD, median, quartiles, minimum, and maximum) and categorical variables by frequencies and percentages.

In this study, the eligible patients will be initially randomized at day 1, and then a re-randomization will occur at week 12 for those patients in groups 2 and 3. The treatment groups will be assigned at each randomization as described in section 3.1.

In general, data will not be imputed for the safety analysis. Efficacy analysis imputations will use the last observation carried forward (LOCF) procedure for patients in analysis populations as described section 9.3.1. Sensitivity analyses on the primary endpoint will be performed to assess the effect of missing data. Details will be described in the SAP and finalized before database lock. 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 the treatment groups for each randomization for the SAF, and the "FAS Secondary Randomization" populations, depending on the type of data. Medical history will be coded by Medical Dictionary for Regulatory Affairs (MedDRA®) codes and prior and concomitant medications by the Anatomical Therapeutic Chemical codes of the World Health Organization Drug Dictionary. No formal comparison between treatment groups will be conducted.

9.5.2. Efficacy Analyses

Efficacy analyses of all the efficacy variables at week 12 defined in section 8.2 will be conducted using the FAS population, and at week 36 using both the FAS and the "FAS Secondary Randomization" populations. The analysis on the FAS will be performed according the treatment assigned at baseline (as randomized). The week 36 analysis will be performed according to the treatment assigned (as re-randomized) at week 12 for group 2 (REGN910-3 high-dose), and group 3 (IAI alone), or at baseline for group 1 (REGN910-3 low-dose). Patients who are not re-randomized will be analyzed by the treatment assigned at baseline.

9.5.2.1. Primary Efficacy Analysis

The efficacy analysis for the primary efficacy endpoint will be the comparison between the REGN910-3 and IAI groups in the mean change in BCVA from baseline to week 12 through week 36. An analysis of covariance model with treatment as the main effect and baseline BCVA measurement as covariates will be employed to calculate the least squares mean and the 2-sided 95% confidence interval of the treatment difference. For patients receiving additional treatment, their assessments will be censored from the next visit after the first additional treatment. Missing values on or before the visit receiving additional treatment will be imputed using the LOCF procedure.

9.5.2.2. Secondary Efficacy Analysis

Additional comparisons will be made between the REGN910-3 and IAI groups with respect to the secondary efficacy variables, as described in section 8.2.

- Change from baseline in CST at week 12 through week 36
- Change in CNV area from baseline at week 12 through week 36
- Change in total lesion area from baseline at week 12 through week 36

The analysis of the secondary endpoints will be performed using the same methodology as for the analysis of the primary efficacy endpoints described in section 9.5.2.1.

9.5.2.3. Additional Efficacy Analyses

Additional comparisons will be made between the REGN910-3 and IAI groups with respect to the additional efficacy variables, as described in section 8.2.1.

- Proportion of patients with no retinal and/or subretinal fluid at week 12 through week 36

- Time to no retinal and/or subretinal fluid

For the categorical additional efficacy variable, a 2-sided 95% confidence interval using normal approximation for the treatment difference will be provided. Time-to-event data will be analyzed using the Kaplan-Meier method. A complete list of additional efficacy variables will be included in the SAP.

9.5.3. Safety Analysis

9.5.3.1. Adverse Events

Definitions

Safety variables will be summarized for the period from baseline/day 1 to the end of the study (week 36).

A treatment-emergent adverse event (TEAE) is defined as an event (or an exacerbation of a pre-existing event) that is observed or reported after the first, and not later than 30 days, after the last administration of study medication.

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 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 treatment, and injection procedure (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. 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.

9.5.3.3. Treatment Exposure

Exposure to study drug will be examined for each patient. The total number of treatments administered and duration of the treatment for each patient in the study will be analyzed and summarized using descriptive statistics by treatment group through week 12 and week 36.

9.5.3.4. Treatment Compliance

Compliance with protocol-defined study medication through week 12 and week 36 will be calculated as follows:

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

9.5.3.5. Additional Treatment

Beginning at week 12, if, in the investigator's judgement, the patient cannot adhere to the protocol-specified dosing interval due to persistent or worsening disease and requires an interim injection, the patient may receive additional treatment. Patients will receive IAI 2 mg if it is determined that additional treatment will be administered. Additional treatment will be summarized as follows:

- Total number of patients that received additional treatment by treatment group
- Total number of injections given as additional treatment to each treatment group beginning at week 12

9.5.4. Analysis of Drug Concentration Data

The concentrations of REGN910 in serum, and concentrations of free aflibercept and adjusted bound aflibercept in plasma will be analyzed to include descriptive statistics at each sampling time.

No formal statistical analysis will be performed.

9.5.5. Analysis of Anti-drug Antibody Data

Listings of ADA positivity titers presented by patient, time point and dose group will be provided. Prevalence of pre-existing treatment-emergent and treatment-boosted ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts.

The influence of ADAs on individual drug concentration over time profiles will be evaluated. Assessment of ADAs on safety and efficacy may be provided.

9.6. 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

Definition of baseline at week 12:

- For efficacy analyses after week 12, the new baseline is defined as the measurement at week 12

General rules for handling missing data:

- Rules for handling missing data for efficacy assessments are addressed in Section 9.5.2.1.
- 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 case report form (CRF) assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with non-protocol 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.

9.7. 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 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
- Medidata RAVE 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, CRO 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/EC 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/EC. A copy of the IRB/EC-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 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/Ethics Committee

An appropriately constituted IRB/EC, 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/EC 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/EC 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/EC approval letter with a current list of the IRB/EC 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/EC 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/EC-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/EC 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

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Double-Masked, Active-Controlled, Phase 2 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal REGN910-3 in Patients with Neovascular, Age-Related Macular Degeneration, 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/EC. 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)

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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 pre-clinical 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 pre-clinical 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 .

Study Title: A Randomized, Double-Masked, Active-Controleed Phase 2 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal REGN910-3 in Patients with Neovascular Age-Related Macular Degeneration

Protocol Number: REGN910-3-AMD-1517.03

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-00015388 v1.0

Approval	[redacted]
Approval	[redacted]
Approval	[redacted]
Approval	[redacted]

Signature Page for VV-RIM-00015388 v1.0 Approved