NCT03022292
Clinical Study Protocol

The IAI-OCTA Study

Compound:	Intravitreal Aflibercept Injection
Study Name:	The IAI-OCTA Study, or: Microvascular structure and morphology of neovascular membranes in age related macular degeneration (AMD) after intravitreal aflibercept injection (IAI) therapy using OCT-Angiography Analysis
Clinical Phase:	VI
Date of Issue:	Version 6 January 03, 2018
Primary Investigator:	David Sarraf, MD

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE:

Micro-vascular structure and morphology of neovascular membranes in age-related macular degeneration (AMD) after intravitreal aflibercept injection (IAI) therapy using OCT-Angiography (OCTA).

TITLE IN LAY TERMS: The IAI-OCTA Study

SITE LOCATION(S):

Stein Eye Institute of UCLA
200 Stein plaza
Los Angeles, CA 90095

Primary Investigator: David Sarraf, MD

OBJECTIVE(S):

To assess and evaluate OCTA technology as an instrument to identify and analyze the growth of untreated type 1, 2, and 3 neovascular membranes in treatment naïve AMD subjects.
To assess and evaluate OCTA technology as an instrument to evaluate the treatment outcomes of IAI in neovascular lesions in AMD.
To identify OCTA parameters or biomarkers of neovascular activity after IAI in AMD.
To better understand the morphology of angiogenesis and arteriogenesis and its response to IAI using OCT angiography analysis.

STUDY DESIGN:

Prospective clinical trial of AMD subjects with neovascularization (type 1, 2 or 3) that have not been treated with prior anti-VEGF therapy in one or both eyes. These subjects will undergo imaging of both eyes with OCT angiography at baseline upon entering this study. Subjects will be scheduled for intravitreal aflibercept injections (IAI) at baseline, week 4, week 8, week 16 week 24, week 36, and week 48. Additional injections can be administered on an as needed basis per Primary Investigator (PI) discretion during the remaining visits. Each subject will therefore receive a minimum of 7 injections and up to a maximum of 13 injections throughout the study period. There will be no injection at the Exit Visit. OCT angiography and spectral domain OCT imaging will be performed at baseline and every 4 weeks thereafter. A subgroup of willing subjects will undergo OCT angiography every 2 weeks for the first 12 weeks. Fluorescein and indocyanine angiography, as well as Fundus Autofluorescence will be performed at baseline. Fundus Autofluorescence and fluorescein angiography will also be performed at week 12 and at week 52 for all subjects. All imaging files for each subject including OCT, OCTA, FA and ICG will be forwarded to a reading center (Doheny Image Reading Research Laboratory or DIRRL) for evaluation and analysis. Detailed OCT angiography analysis will be performed to identify anatomical and morphological biomarkers of growth progression and disease activity, which may guide treatment in the future and may help to develop more effective therapies that may target resistant and recalcitrant neovascular lesions that continue to grow, leak, and scar despite maximum intravitreal anti-VEGF therapy.

In addition to qualitative structural and morphological analysis of all neovascular lesions at baseline and follow up, detailed quantitative OCT angiographic analysis of the neovascular lesion using automated or manual capillary density maps and area calculation will be performed at each visit to determine the detailed microvascular response of neovascular complexes to IAI therapy.

STUDY DURATION: 1 YEAR

ESTIMATED STUDY COMPLETION DATE: DECEMBER 2018

POPULATION

Sample Size: 30 subjects.

Target Population: Male and female subjects over the age of 50 with naïve wet macular degeneration in one or both eyes.

TREATMENT(S)

Study Drug: Intravitreal aflibercept injection (2 mg/ 0.05 ml)

Dose/Route/Schedule: Subjects will be scheduled for intravitreal aflibercept 2mg/ 0.05 ml injection at baseline, week 4, week 8,, week 16, week 24, week 36, and week 48. Additional injections can be administered during the remaining visits on an as needed basis per PI discretion based on the presence of any intraretinal or subretinal fluid on OCT, heme visualized on examination, reduction of BCVA by 5 or more ETDRS letters, or evidence of either increased area, density, or activity of the brush border of the neovascularization on OCT-angiography. There will be a minimum of 21 days between subsequent injections. Each subject will therefore receive a minimum of 7injections and up to a maximum of 13 injections throughout the study period. There will be no injection at the exit visit, week 52.

ENDPOINT(S)

Primary: OCT angiography % of neovascular membrane as measured by area of the neovascular lesion (in millimeters^2) and vessel density (in millimeters^{-1}) at 24 weeks

Secondary: Endpoints will be evaluated at 24 weeks and 52 weeks, unless indicated:

- OCT angiography % regression of neovascular membrane as measured by area of the neovascular lesion (in millimeters^2) and vessel density (in millimeters^{-1}) at 52 weeks
- Mean best corrected visual acuity (BCVA)
- Proportion of patients with gain of ≥5, ≥10, or ≥15 ETDRS letters
- Mean number of injections
- Status of SD OCT intraretinal and subretinal fluid and subretinal hyper-reflective material (SHRM)
- Change in SD OCT central macular thickness, volume of subretinal fluid, volume of SHRM, severity of cystoid macular edema, volume of pigment epithelial detachment (PED), and height of PED
- OCT angiography qualitative analysis of the structural microvascular anatomy and morphological biomarkers of the neovascular complex including attenuation of the fringe, presence of flow-void areas, and changes in vessel looping
- Incidence and severity of ocular and systemic adverse events
- FAF monitoring of atrophy development from baseline to week 12, to week 52

Exploratory: (In subjects participating in the sub-study of serial OCT Angiography during the initial 12 weeks)

- OCT angiography % regression of neovascular membrane as measured by area of the neovascular lesion (in millimeters^2) and vessel density (in millimeters^{-1}) during the initial 12 weeks
- OCT angiography qualitative analysis of morphological biomarkers of the neovascular complex including attenuation of the fringe, presence of flow-void areas, and changes in vessel looping during the initial 12 weeks

PROCEDURES AND ASSESSMENTS:

Informed Consent, Inclusion/Exclusion Criteria Assessment, Medical/Surgical/Ocular History review, Demographic Information review, Tobacco history review, and Concomitant Medication review, OCT Angiography, Spectral Domain OCT, Fluorescein Angiography, Indocyanine Green Angiography imaging, Fundus Photography, vital signs at baseline, Best Corrected Visual Acuity Exam, Intraocular Pressure Evaluation, Slit Lamp Evaluation, Dilated Fundus Exam, Study Drug Administration, and Post Injection Intraocular Pressure and Vision Assessment

STATISTICAL PLAN:

Parametric and possibly nonparametric tests may be conducted to calculate for statistical significance in assessing the differences of the posterior-treatment values from the baseline values during the first 6 months in comparison with the second 6 months of the study, depending on the variables. The significance level to be used is alpha $\leq$ 0.05. Statistical analysis will be performed on data from all subjects in this study by the staff statistician, Fei Yu.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
CRF	Case Report Form
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event

1. INTRODUCTION AND RATIONALE

1.1 Introduction

Neovascular age-related macular degeneration (AMD) is the leading cause of adult blindness [1]. While anti-VEGF therapy significantly reduces the rate of severe vision loss and may improve vision, subjects with choroidal neovascularization (CNV) continue to lose vision long-term and experience an eventual decay in visual acuity [2]. Recent advancements in OCT-Angiography (OCTA) have enabled for the first time the ability to directly identify and analyze the detailed microvascular structure and morphology of neovascular complexes in AMD [3-6]. OCTA utilizes amplitude or phase decorrelation technology with high-frequency and dense volumetric scanning to detect red blood cell movement and to visualize blood vessels at depth resolved levels throughout the retina and choroid [3]. OCTA enables more accurate identification of neovascular lesions compared to traditional fluorescein angiography (FA). Historically, FA findings such as irregular elevation of the RPE with stippled fluorescence were interpreted to suggest the presence of occult choroidal neovascularization (CNV) [7]. As opposed to FA where vessel leakage and blurred edges lead one to infer the presence of occult CNV, OCTA reveals the vessels themselves and enables more accurate identification of the morphology of the neovascular complex and monitoring of its structural response to therapy.

OCTA therefore may provide critical information relating to the development and progression of neovascularization in AMD and the response of these lesions to anti-VEGF therapy. Identifying biomarkers of neovascular activity and progression using OCTA may provide further guidance and advancement in the management of neovascular AMD, may provide better outcome parameters for clinical trials that study neovascular AMD therapy, and may permit the development of more effective therapeutic agents for neovascular AMD.

1.2 Rationale

1.2.1 Rationale for Study Design

Previous clinical trials have not been able to analyze the complex microvascular anatomy of the various forms of neovascular lesions in AMD. With the advent of OCTA, we are able to directly assess the microvascular morphology and structural architecture of neovascular membranes that occur in AMD and assess the responsiveness of these neovascular membranes to anti-VEGF therapy [3,7]. Early studies using OCTA in neovascular AMD have shown that type 1 and type 2 neovascular membranes continue to grow and mature despite continued anti-VEGF therapy and develop a resistant and mature core of large dilated feeder vessels that do not respond to any of the approved anti-VEGF agents [3,8-11]. Understanding the development and progression in the growth of these neovascular membranes and determining the detailed microvascular anatomy and structure of these resistant neovascular complexes will spur the development of improved therapeutic options that can more efficaciously treat CNV leading to better long term visual and anatomic outcomes. In addition it is important to identify markers of neovascular activity using OCTA which will better guide therapy in

the future and will provide important parameters to be used for future clinical trials assessing the efficacy of neovascular AMD therapies.

1.2.2 Rationale for Dose Selection

Intravitreal aflibercept injection 2mg/0.05ml is the standard FDA approved dose that has been used in previous Phase III trials and has been shown to be effective [12].

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to assess the % regression of choroidal neovascular membrane as measured by area of the neovascular lesion (in millimeters^2) and vessel density (in millimeters^{-1}) using OCT angiography at 24 weeks while subjects receive IAI therapy in follow up.

2.2 Secondary Objective(s)

The secondary objectives of the study are to assess the following at 24 weeks and 52 weeks, unless indicated:

- The % regression of choroidal neovascular membrane as measured by area of the neovascular lesion (in millimeters^2) and vessel density (in millimeters^{-1}) using OCT angiography at 52 weeks
- Mean best corrected visual acuity (BCVA)
- Proportion of patients with gain of ≥5, ≥10, or ≥15 ETDRS letters
- Mean number of injections
- Status of SD OCT intraretinal and subretinal fluid and subretinal hyper-reflective material (SHRM)
- Change in SD OCT central macular thickness, volume of subretinal fluid, volume of SHRM, severity of cystoid macular edema, volume of pigment epithelial detachment (PED), and height of PED
- OCT angiography qualitative analysis of the structural microvascular anatomy and morphological biomarkers of the neovascular complex including attenuation of the fringe, presence of flow-void areas, and changes in vessel looping
- Incidence and severity of ocular and systemic adverse events
- FAF monitoring of atrophy development from baseline to week 12, to week 52

2.3 Exploratory Objective(s)

The exploratory objectives of the study are to assess the following for subjects participating in the sub-study of serial OCT angiography during the initial 12 weeks:

- OCT angiography % regression of choroidal neovascular membrane as measured by area of the neovascular lesion (in millimeters^2) and vessel density (in millimeters^{-1}) during the initial 12 weeks
- OCT angiography qualitative analysis of morphological biomarkers of the neovascular complex including attenuation of the fringe, presence of flow-void areas, and changes in vessel looping during the initial 12 weeks

3. STUDY DESIGN

3.1 Study Description and Duration

Prospective clinical trial of neovascular AMD subjects with type 1, 2, or 3 neovascularizationin one or both eyes that have not been treated with prior anti-VEGF therapy. These subjects will undergo imaging of both eyes with OCTA at baseline upon entering this study. Subjects will be scheduled for intravitreal aflibercept injection (IAI) at baseline, week 4, week 8, week 16, week 24, week 36, and week 48. Additional injections can be administered during the remaining visits on an as needed basis per PI discretion based on the presence of any intraretinal or subretinal fluid on OCT, heme visualized on examination, reduction of BCVA by 5 or more ETDRS letters, or evidence of either increased area, density, or activity of the brush border of the neovascularization on OCT angiography. There will be a minimum of 21 days between subsequent injections. Each subject will therefore receive a minimum of 7 injections per enrolled eye and up to a maximum of 13 injections throughout the study period per enrolled eye. No injection will be given on the exit visit, week 52. OCT angiography and spectral domain OCT imaging will be performed at baseline and every 4 weeks thereafter.

A subgroup of willing subjects will undergo OCT angiography every 2 weeks for the first 12 weeks.

Indocyanine green angiography will be performed at baseline for all subjects to establish baseline subject population characteristics. Fluorescein angiography will be performed at baseline, week 12, and week 52 for efficacy monitoring. Detailed OCT angiography analysis will be performed to identify anatomical and morphological biomarkers of growth progression and disease activity. In addition to qualitative structural and morphological analysis, detailed quantitative OCT angiography analysis of the neovascular lesion using automated or manual capillary density maps and area calculation will be performed at each visit to determine the detailed microvascular response of neovascular complexes to IAI therapy.

3.2 Planned Interim Analysis

There is no planned interim analysis for this study. However, interim analyses may be performed in order to summarize preliminary results for the purpose of abstract submission for presentation at national or international meetings. Adverse event reports from this study may be reviewed and summarized periodically throughout the study to ensure the safety of subjects.

3.3 Study Committees

3.3.1 Independent Data Monitoring Committee

All imaging files for each subject including OCT, OCTA, FA and ICG will be forwarded to a reading center (Doheny Image Reading Research Laboratory or DIRRL) for evaluation and analysis.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

4.1 Number of Subjects Planned

30 subjects will be included in this study.

4.2 Study Population

Male and female subjects over the age of 50 with treatment-naïve wet macular degeneration in one or both eyes.

4.2.1 Inclusion Criteria

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

1. Subject is older than 50 years of age.
2. Subject is willing to participate in the study and able to follow the study criteria and protocol.
3. The study eye is treatment naive regarding treatment of neovascular AMD.
4. Subject is willing and able to comply with clinic visits and study-related procedures.
5. Subject is able to provide signed informed consent.
6. Subject is able to understand and complete study-related questionnaires.
7. The subject is not currently involved with any other clinical study.
8. Best Corrected Visual Acuity (BCVA) with ETDRS Snellen equivalent of 20/400 or better and 20/32 or worse in the study eye.
9. Sufficiently clear media (cornea, anterior chamber, lens, vitreous) for OCT, FA and fundus photography (FP) in the study eye.
10. Intraocular pressure (IOP) of 25mmHg or less in the study eye, with or without use of ocular hypotensive agents.
11. Prior focal corticosteroid treatment is allowed, as long as the study eye is not involved. However prior (within 90 days of Day 0) or current systemic corticosteroid therapy (oral or intravenous corticosteroid treatment) is not permitted.

4.2.2 Exclusion Criteria

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

1. Any prior treatment of neovascular AMD in the eye proposed for enrollment including previous anti-vascular endothelial factor (anti-VEGF) therapy, photodynamic therapy (PDT), radiation therapy, corticosteroid treatment, surgical treatment for CNV, thermal laser treatment, and any other prior intravitreal treatment for neovascular AMD (except minerals and vitamins).
2. Known serious allergies to aflibercept, fluorescein dye, Indocyanine Green (ICG), shellfish, drugs for pupillary dilation, topical anesthetic, or sterilizing solution (e.g. Betadine Solution).
3. Prior or current systemic anti-VEGF therapy.
4. Pregnant or breast-feeding women.

5. Sexually active men* or women of childbearing potential** who are unwilling to practice adequate contraception during the study (adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly).
6. Contraindication to pupillary dilation in study eye.
7. Any condition (including inability to read visual acuity charts, or language barrier) that may preclude subjects ability to comply with the study protocol and requirements.
8. Presence of any advanced systemic condition or end-stage disease, such as advanced Alzheimer Syndrome, end-stage cancer, etc., which will likely prevent subject from completing study.
9. Previous therapeutic radiation in the region of the study eye.
10. Prior retinal pigment epithelial (RPE) tear in study eye.
11. Prior ocular surgery (except YAG laser capsulotomy) for study within the past 90 days.
12. Anticipated ocular surgery (except YAG laser capsulotomy) for the next 12 months.
13. Prior vitrectomy in the study eye.
14. Presence of any causes of CNV and PED other than due to AMD or presence of ocular disease other than AMD affecting study eye, i.e. presumed ocular histoplasmosis syndrome, android streaks, pathologic myopia (spherical equivalent of ≥ -8 diopters of myopia or axial length of ≥ 25mm), choroidal rupture, multifocal choroiditis, etc.
15. Presence of any substantial ocular disease (other than the CNV and PED) that may compromise vision in the study eye and/or confound interpretation of the data; e.g. substantial cataracts, concomitant diabetic retinopathy affecting the macula, advanced glaucoma, optic neuritis, optic neuropathy, or atrophy, marked macular atrophy, ocular vascular occlusion, history of retinal detachment, uveitis, viral or other forms of chorioretinitis, etc.
16. Active ocular infection (i.e., bacterial, viral, parasitic, or fungal) in either eye at screening
17. Serous PED without neovascularization and polypoidal choroidal vasculopathy (PCV) lesions are excluded in the study eye.
18. PED ≥ 12 disc areas in size.
19. Surface area of submacular hemorrhage >50% of entire PED, if present in the study eye.
20. Submacular fibrosis >50% of the entire PED, if present in the study eye.

*Contraception is not required for men with documented vasectomy.

Postmenopausal women must be amenorrheic for at least 12 months in order **not to be considered of child bearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

4.3 Premature Withdrawal from the Study

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

The investigator has the right to withdraw a subject from the study in the event of an intercurrent illness, 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 subjects will be avoided.

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

4.4 Replacement of Subjects

Subjects prematurely withdrawn from the study can be replaced, if needed, to ensure an adequate number of evaluable subjects. The investigator, in cooperation with the study statistician, will decide whether or not to replace withdrawn subjects.

5. STUDY TREATMENTS

5.1 Investigational Treatment

Intravitreal injection of aflibercept 2 mg/0.05 ml at baseline, week 4, week 8, week 16, week 24, week 36, and week48. Additional injections can be administered during the remaining visits on an as needed basis per Primary Investigator (PI) discretion based on the presence of any intraretinal or subretinal fluid on OCT, heme visualized on examination, reduction of BCVA by 5 or more ETDRS letters, or evidence of either increased area, density, or activity of the brush border of the neovascularization on OCT-angiography. There will be a minimum of 21 days between subsequent injections. Each subject will therefore receive a minimum of 7 injections and up to a maximum of 13 injections throughout the study period.

5.2 Dose Modification and Stopping Rules

5.2.1 Dose Modification

Dose modification for an individual subject is not allowed.

5.2.2 Study Drug Stopping Rules

5.2.2.1 Reasons for Permanent Discontinuation of Study Drug

Subjects have a right to withdraw from the study at any time.

The subject may be withdrawn from the study for any reasons: if it is in the best interest of the subject, serious concurrent illnesses, adverse events, or worsening condition. Dr.

David Sarraf and staff may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

If a subject discontinues from the study, he or she will not be allowed to re-enter the study.

Reasons for subject discontinuation may include, but are not limited to, the following:

- Sensory rhegmatogenous retinal detachment or Stage 3 or 4 macular hole
- Investigator determination that it is not in the best interest of the subject to continue participation
- Pregnancy
- Verteporfin PDT treatment in the study eye
- Pegaptanib sodium injection in either eye
- Bevacizumab injection in either eye
- Ranibizumab injection in either eye
- SAE
- Any other safety concerns

In the event of an adverse event in the study eye that is considered by the investigator to be severe in intensity, serious consideration should be given to discontinuing the subject from the study.

5.3 Treatment Logistics and Accountability

5.3.1 Packaging, Labeling, and Storage

A medication numbering system will be used in labeling investigational study drug, displaying the product lot number on the label. Lists linking medication numbers with product lot numbers will be maintained by the Investigational Drug Pharmacy of UCLA located at 757 Westwood Plaza, Room B524.

Study drug will be refrigerated at the site at a temperature of 2 to 8ºC; refrigerator temperature will be logged daily. At no time, will product be left unattended or outside the control of an individual knowledgeable with regard to product temperature requirements. Failure to maintain 2° to 8°C temperature control will likely result in unusable product. Moreover, no one will administer product that has not been maintained according to temperature requirements.

5.3.2 Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2 to 8ºC to the investigator or designee at regular intervals or as needed during the study. During site close-out, and following drug reconciliation and documentation, all opened and unopened vials of study drug will be destroyed or returned to Regeneron Pharmaceuticals, Inc. or designee.

5.3.3 Treatment Accountability

All drug accountability records will be kept current.

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

- dispensed to each subject,
- returned from each subject (if applicable), and
- disposed of at the site or returned to Regeneron Pharmaceuticals, Inc. or designee.

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

5.3.4 Treatment Compliance

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

5.4 Concomitant Medications and Procedures

At the screening visit, the subject will be asked to disclose the names of any concomitant medications they are taking as well as any medical procedures they have undergone in the past. During every subsequent visit, the subject will be asked about any changes to medications or new procedures they received between study visits.

5.4.1 Permitted Medications and Procedures

Subjects may continue to take any existing concomitant medications with the exception of the prohibited medications and procedures as shown below. Topical eye drops for dry eye, controlled glaucoma, or allergic conjunctivitis are permissible. Prior or ongoing treatment of the fellow eye with intravitreal aflibercept injection is also permitted.

5.4.2 Prohibited Medications and Procedures

Subjects must not have taken on any oral or intravenous anti-VEGF drugs within 6 months of study procedures. Subjects must not be on any form of chemotherapy, radiation therapy, intravenous corticosteroid drugs within 6 months of study procedures. Subjects must not have participated with any other clinical trials within past 6 months.

5.5 Post-Study Treatment

Post study completion, subjects will be released to standard of care clinical treatment and observation with a Retina Specialist. Care may be maintained clinically under the PI.

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	Screen/ Baseline	Week 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Week 52Exit/Early Termination
(+/- Day Window)	-14 to 0 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Inclusion/Exclusion	X																
Informed Consent	X																
Medical History	X																
Surgical History	X																
Demographics	X																
Tobacco History	X																
Administer Study Drug	X		X		X		prn	X	prn	X	prn	prn	X	prn	prn	X	
Concomitant Meds and Tx	X		X		X		X	X	X	X	X	X	X	X	X	X	X
BCVA Exam	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Slit Lamp Evaluation	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Dilated Fundus Exam	X		X		X		X	X	X	X	X	X	X	X	X	X	X
SD-OCT	X		X		X		X	X	X	X	X	X	X	X	X	X	X
OCT-Angiography	X	X*	X	X*	X	X*	X	X	X	X	X	X	X	X	X	X	X
FAF Imaging**	X						X										X
FA	X						X										X
ICG Imaging	X																
Adverse Events			X		X		X	X	X	X	X	X	X	X	X	X	X
IOP, Pre-dose	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Post-dose VA and IOP	X		X		X		prn	X	prn	X	prn	prn	X	prn	prn	X	

*A subgroup of willing subjects will undergo OCTA every 2 weeks for the first 12 weeks. **For subjects enrolled prior to inclusion of FAF, FAF will be performed at next scheduled visit or beginning at Week 12 (whichever is soonest after protocol approval).

6.2 Study Visit Descriptions

6.2.1 Screening/Baseline/Day 1 (-14 to 0 days)

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

- Inclusion/exclusion Criteria Review
- Demographics and Tobacco History
- Medical history, surgical history, and concurrent illnesses
- Concomitant medications

The following procedures and assessments will be conducted:

- BCVA Exam
- IOP Assessment
- Slit-lamp Examination
- Dilated Fundus Examination
- SD-OCT
- OCT-angiography
- FAF Imaging
- Fluorescein Angiography
- ICG Imaging
- Study Drug Administration
- Post Procedure VA and IOP

6.2.2 Week 2 (+/- 7 days), Week 6 (+/- 7 days), Week 10 (+/- 7 days)

The following procedure will be conducted on a subgroup of willing subjects:

- OCT-angiography

6.2.3 Week 4 (+/- 7 days) and Week 8 (+/- 7 days)

The following information will be collected:

- Concomitant medications
- Adverse Events

The following procedures and assessments will be conducted:

- BCVA Exam
- IOP Assessment
- Slit-lamp Examination
- Dilated Fundus Examination
- SD-OCT

- OCT-angiography
- Study Drug Administration
- Post Procedure VA and IOP

6.2.4 Week 12 (+/- 7 days)

The following information will be collected:

- Concomitant medications
- Adverse Events

The following procedures and assessments will be conducted:

- BCVA Exam
- IOP Assessment
- Slit-lamp Examination
- Dilated Fundus Examination
- SD-OCT
- OCT-angiography
- FAF Imaging
- FA imaging

The following procedures will be conducted on an AS NEEDED basis per PI discretion based on the presence of any intraretinal or subretinal fluid on OCT, heme visualized on examination, reduction of BCVA by 5 or more ETDRS letters, or evidence of either increased area, density, or activity of the brush border of the neovascularization on OCT-angiography:

- Study Drug Administration
- Post Procedure VA and IOP

6.2.5 Week16 (+/-7 days), Week 24 (+/- 7 days),Week 36 (+/- 7 days), and Week 48 (+/- 7 days)

The following information will be collected:

- Concomitant medications
- Adverse Events

The following procedures and assessments will be conducted:

- BCVA Exam
- IOP Assessment
- Slit-lamp Examination
- Dilated Fundus Examination
- SD-OCT

- OCT-angiography
- Study Drug Administration
- Post Procedure VA and IOP

6.2.6 Week 20 (+/- 7 days), Week 28 (+/- 7 days), Week 32 (+/- 7 days), and Week 40 (+/- 7 days), and week 44 (+/- 7days)

The following information will be collected:

- Concomitant medications
- Adverse Events

The following procedures and assessments will be conducted:

- BCVA Exam
- IOP Assessment
- Slit-lamp Examination
- Dilated Fundus Examination
- SD-OCT
- OCT-angiography

The following procedures will be conducted on an AS NEEDED basis per PI discretion based on the presence of any intraretinal or subretinal fluid on OCT, heme visualized on examination, reduction of BCVA by 5 or more ETDRS letters, or evidence of either increased area, density, or activity of the brush border of the neovascularization on OCT-angiography:

- Study Drug Administration
- Post Procedure VA and IOP

6.2.7 End of Study Visit/Early Termination/Week 52 (+/- 7 days)

The following information will be collected:

- Concomitant medications
- Adverse Events

The following procedures and assessments will be conducted:

- BCVA Exam
- IOP Assessment
- Slit-lamp Examination
- Dilated Fundus Examination
- SD-OCT
- OCT-angiography
- FAF Imaging

- FA Imaging

6.2.8 Early Termination Visit

Subjects who are withdrawn from the study prior to completion should return to the clinic for an early termination evaluation 4 weeks (± 2 weeks) following the last injection/study visit for monitoring of all adverse events. The schedule of assessments for early termination is the same as that for the final visit.

6.2.9 Unscheduled Visits

All attempts should be made to keep subjects 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.

6.3 Study Procedures

6.3.1 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.

6.3.1.1 Demographic, Medical History, Tobacco History, and Surgical History Review

The above listed items will be reviewed with subjects after the informed consent has been signed for the purpose of establishing subject population characteristics at baseline.

6.3.1.2 ICG Imaging

ICG imaging will take place at baseline only as a means of establishing baseline subject population characteristics.

6.3.2 Efficacy Procedures

6.3.2.1 Visual Acuity

BCVA will be assessed on an ETDRS chart at a starting distance of 4 m (performed prior to dilating eyes).

6.3.2.2 SD-OCT

Spectral Domain Optical Coherence Tomography will be used every 4 weeks starting at Baseline visit for efficacy monitoring.

6.3.2.3 OCT-Angiography

OCT-Angiography will be used every 4 weeks starting at Baseline visit for efficacy monitoring.

6.3.2.4 Fluorescein Angiography

Fluorescein angiography will be obtained at Baseline visit, Week 12, and at Study Exit for efficacy monitoring.

6.3.2.5 Fundus Autofluorescence

Fundus Autofluorescence will be performed at Baseline, Week 12, and at Study Exit for efficacy monitoring.

6.3.3 Safety Procedures

6.3.3.1 Adverse Event Information Collection

The investigator (or designee) will record all AEs that occur during the study from baseline through End of Study Visit or Early Termination on the AE pages of the case report form (CRF). Information on follow-up for AEs is provided in Section 7.2.5. Laboratory or vital signs abnormalities are to be recorded as AEs as outlined in Section 7.2.

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

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1 Definitions

7.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (i.e. any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

7.1.2 Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (e.g. a car accident in which a subject is a passenger).
- Is **life-threatening** – in the view of the investigator, the subject 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 inpatient **hospitalization** or prolongation of existing hospitalization. Inpatient 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 subject or may require intervention to prevent 1 of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse). Any malignancy (other than basal cell skin cancers) would be considered a medically important event.

7.2 Recording and Reporting Adverse Events

All AEs and SAEs will be recorded on the CRF and in the subject's source documents. Laboratory or vital signs abnormalities will be recorded as AEs only if they are medically relevant.

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

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

7.2.1 Deaths

Any AE that results in death is considered an SAE. Deaths that occur from the time the subject signs the informed consent form ("ICF") until 28 days after dosing will be reported to the appropriate IRB and to Regeneron Pharmacovigilance and Risk Management (or designee) within 24 hours of learning of the death.

Any available autopsy reports and relevant medical reports will be sent to Regeneron Pharmaceuticals, Inc. as soon as possible.

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

Medical.safety@regeneron.com
Fax 914-345-7476
SAE hotline: 914-593-1504

7.2.2 Pregnancy and Other Events that Require Accelerated Reporting

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

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

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

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

Medical.safety@regeneron.com
Fax 914-345-7476
SAE hotline: 914-593-1504

7.2.3 Reporting Adverse Events Leading to Withdrawal from the Study

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

Medical.safety@regeneron.com
Fax 914-345-7476
SAE hotline: 914-593-1504

7.2.4 Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

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

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

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

7.2.5 Follow-up

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

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

7.3 Evaluation of Severity and Causality

7.3.1 Evaluation of Severity

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

- **Mild:** Does not interfere in a significant manner with the subject'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 subject.
- **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 subject's health. Treatment for symptom may be given and/or subject hospitalized.

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

7.3.2 Evaluation of Causality

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

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

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

8. STUDY VARIABLES

8.1 Demographic and Baseline Characteristics

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

8.2 Primary, Secondary, and Exploratory Endpoints

The primary endpoint in the study is the OCT angiography % regression of choroidal neovascular membrane as measured by area of the neovascular lesion (in millimeters^{2}) and vessel density (in millimeters^{-1}) at 24 weeks.

The following secondary endpoints will be evaluated at 24 weeks and 48 weeks, unless indicated:

- The % regression of choroidal neovascular membrane as measured by area of the neovascular lesion (in millimeters^{2}) and vessel density (in millimeters^{-1}) using OCT angiography at 48 weeks

- Mean best corrected visual acuity (BCVA)
- Proportion of patients with gain of ≥5, ≥10, or ≥15 ETDRS letters
- Mean number of injections
- Status of SD OCT intraretinal and subretinal fluid and subretinal hyper-reflective material (SHRM)
- Change in SD OCT central macular thickness, volume of subretinal fluid, volume of SHRM, severity of cystoid macular edema, volume of pigment epithelial detachment (PED), and height of PED
- OCT angiography qualitative analysis of the structural microvascular anatomy and morphological biomarkers of the neovascular complex including attenuation of the fringe, presence of flow-void areas, and changes in vessel looping
- Incidence and severity of ocular and systemic adverse events
- FAF monitoring of atrophy development from baseline to week 12, to week 52

The exploratory endpoints for subjects participating in the sub-study of serial OCT angiography during the initial 12 weeks are the following:

- OCT angiography % regression of choroidal neovascular membrane as measured by area of the neovascular lesion (in millimeters^2) and vessel density (in millimeters^{-1}) during the initial 12 weeks
- OCT angiography qualitative analysis of morphological biomarkers of the neovascular complex including attenuation of the fringe, presence of flow-void areas, and changes in vessel looping during the initial 12 weeks

9. STATISTICAL PLAN

9.1 Determination of Sample Size

There is no formal sample size calculation for this study. A sample size of 30 subjects is chosen, making sure that it is feasible to conduct and complete the study within a reasonable time. Data from all enrolled subjects will be analyzed.

9.2 Statistical Methods

9.2.1 Demography and Baseline Characteristics

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

9.2.2 Efficacy Analyses

9.2.2.1 Primary Efficacy Analysis

Detailed anatomical descriptions and grading of lesion components in a standardized fashion in a reading center setting at baseline and subsequent follow-up visits, including changes in % regression of choroidal neovascular membrane at 24 weeks as measured by area of the neovascular lesion (in millimeters^2) and vessel density (in millimeters^{-1}) using OCT angiography while subjects receive IAI therapy in follow up.

9.2.2.2 Secondary Efficacy Analysis

The following will be calculated at 24 weeks and 48 weeks, unless indicated:

- The % regression of choroidal neovascular membrane as measured by area of the neovascular lesion (in millimeters^2) and vessel density (in millimeters^{-1}) using OCT angiography at 48 weeks
- Mean best corrected visual acuity (BCVA)
- Proportion of patients with gain of ≥5, ≥10, or ≥15 ETDRS letters
- Mean number of injections
- Status of SD OCT intraretinal and subretinal fluid and subretinal hyper-reflective material (SHRM)
- Change in SD OCT central macular thickness, volume of subretinal fluid, volume of SHRM, severity of cystoid macular edema, volume of pigment epithelial detachment (PED), and height of PED
- OCT angiography qualitative analysis of the structural microvascular anatomy and morphological biomarkers of the neovascular complex including attenuation of the fringe, presence of flow-void areas, and changes in vessel looping
- Incidence and severity of ocular and systemic adverse events
- FAF monitoring of atrophy development from baseline to week 12, to week 52

9.2.2.3 Exploratory Efficacy Analysis

The following will be calculated for subjects participating in the sub-study of serial OCT angiography during the initial 12 weeks:

- OCT angiography % regression of choroidal neovascular membrane as measured by area of the neovascular lesion (in millimeters^2) and vessel density (in millimeters^{-1}) during the initial 12 weeks
- OCT angiography qualitative analysis of morphological biomarkers of the neovascular complex including attenuation of the fringe, presence of flow-void areas, and changes in vessel looping during the initial 12 weeks

9.2.3 Safety Analysis

9.2.3.1 Adverse Events

Incidence and severity of ocular and systemic safety events through week 48 including: worsened acuity > 30 letters, retinal detachment, endophthalmitis, cataract progression, vitreous hemorrhage, new PDR or neovascularization of the iris or angle, systemic thromboembolic events, deaths, and systemic serious adverse event.

9.2.4 Interim Analysis

Interim analyses may be performed in order to summarize preliminary results for the purpose of abstract submission for presentation at national or international meetings. Adverse event reports from this study may be reviewed and summarized periodically throughout the study to ensure the safety of subjects.

9.3 Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, all data collected and safety parameters will be summarized.

10. STUDY MONITORING

10.1 Source Document Requirements

Investigator will prepare and maintain adequate and accurate subject records (source documents).

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

10.2 Case Report Form Requirements

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

11. AUDITS AND INSPECTIONS

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

- Informing Regeneron of a planned inspection by the authorities as soon as notification is received
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the Regeneron immediately
- Taking all appropriate measures requested by the regulatory authorities to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection.

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

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Good Clinical Practice Statement

It is the responsibility of the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

12.2 Informed Consent

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

Regeneron will have the right to review and comment on the informed consent form.

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

Subjects who can write but cannot read will have the ICF read to them before signing and dating the ICF.

Subjects who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

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

If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated appropriately. All study subjects will be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF will be maintained in the subject's study record and a copy will be given to the subject.

12.3 Subject Confidentiality and Data Protection

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

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

12.4 Institutional Review Board

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

- The protocol, ICF, and any other materials to be provided to the subjects (e.g. advertising) before any subject may be enrolled in the study

- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the IRB will be informed as soon as possible

Ongoing studies will be reviewed by the IRB on an annual basis or at intervals appropriate to the degree of risk.

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

A copy of the IRB approval letter will be sent to Regeneron prior to shipment of drug supplies to the investigator. The approval letter will include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB review and approval of all study documents (including approval of ongoing studies) will be kept on file by the investigator.

13. PROTOCOL AMENDMENTS

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

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

14.1 Premature Termination of the Study

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

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

15. STUDY DOCUMENTATION

15.1 Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs will be signed by the investigator. This certification form accompanies each set of CRFs.

15.2 Retention of Records

The investigator will retain all essential study documents, including ICFs, source documents, 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. Records will be destroyed in a manner that ensures confidentiality.

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