IND Number: 12462 Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, SINGLE-MASKED, ACTIVE-CONTROLLED PHASE 2 STUDY OF THE SAFETY, TOLERABILITY, AND EFFICACY OF REPEATED DOSES OF HIGH-DOSE AFLIBERCEPT IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Compound:	High Dose Aflibercept
Clinical Phase:	2
Protocol Number:	VGFTe (HD)-AMD-1905
Protocol Version:	VGFTe (HD)-AMD-1905 Amendment 3
Amendment 3 Date of Issue:	*See appended electronic signature page*
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AMENDMENT HISTORY

AMENDMENT 3

The purpose of this amendment is to change the time point for evaluation of the primary endpoint (proportion of patients without retinal fluid in the center subfield) and certain exploratory endpoints from Week 20 to Week 16. Week 16 is 8 weeks after the third initial loading dose in both treatment groups and represents the earliest timepoint to assess anatomic differences in treatment effect between 2 mg and 8 mg. Since some patients will receive additional dosing at Week 16 while others will not, 20 weeks is less ideal for understanding and comparing treatment effects. This will allow a direct comparison of the 2 treatment groups prior to any Additional/Rescue treatment being administered which could potentially confound interpretation of the results.

Change	Rationale for Change	Sections Changed
Change of the time point for evaluation of the primary endpoint and certain exploratory efficacy endpoints from Week 20 to Week 16.	To allow head-to-head comparison of the 2 treatment arms without potential confounding by additional/rescue treatment. Week 16 is 8 weeks after the third initial loading dose in both treatment groups and represents the earliest timepoint to assess anatomic differences in treatment effect between 2 mg and 8 mg. Since some patients will receive additional dosing at Week 16 while others will not, 20 weeks is less ideal for understanding and comparing treatment effects.	Synopsis: Study Design, Endpoints (Co-primary), Statistical Plan (Statistical Hypothesis, Efficacy Analyses) Section 4.1.1 Primary Endpoints Section 4.1.3 Exploratory Endpoints Section 6.1 Figure 1 Study Flow Diagram Section 6.1 Figure 2 Dosing Schedule Section 9.1.3 Early Termination Visit Section 11.1 Statistical Hypothesis Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Exploratory Efficacy Analysis
Remove reference to "OC" as a method for imputation of missing data.	Correction for accuracy in the Statistical Analysis section.	Section 11.4.3.2 , Exploratory Efficacy Analysis
Removed mention of absence of imputation of missing data in the Safety section.	Correction for accuracy in the Safety Analysis section.	Section 11.4.5 , Safety Analysis

Amendment 2

The purpose of this amendment is to add the option for dense pharmacokinetic (PK) substudy patients to have certain procedures on specified visits performed at a location other than the clinical trial site using a mobile nursing service, to possibly enroll additional patients into the PK substudy, and to add required language related to the "Coronavirus Disease 2019" (COVID-19) pandemic.

Change and Rationale for Change	Sections Changed
Addition of option for mobile healthcare professional service for certain visits for patients in the dense PK substudy, to enable the conduct of the trial during the COVID-19 pandemic. Additional patients may be enrolled in the dense PK portion of the study to ensure adequate data are captured.	Synopsis: Study Design, Population (Sample Size) Section 3.3 Risk-Benefit Section 9.1.1.1 Footnotes for the Schedule of Events for the Study (#19) Section 6.1 Study Description and Duration Section 7.1 Number of Patients Planned Section 8.4 Method of Treatment Assignment Section 9.1.2 Table 2 Schedule of Events (Dense PK Substudy) Section 9.1.2.1 Footnotes for the Schedule of Events for the Dense PK Substudy (#1, #2, #4, #6)
Additional exclusion criterion to clarify COVID-19 standards for study inclusion/exclusion, as required language related to conduct of trials during the pandemic.	Section 7.2.2 Exclusion Criteria (#33)
Clarification to state that the timing of blood pressure (BP) and PK sample collection should be within 2 hours of the time of the injection on day 1 of the study.	Section 9.1.1.1 Footnotes for the Schedule of Events for the Study (#20)

Change and Rationale for Change	Sections Changed
Addition of option for mobile healthcare professional service for certain visits for patients in the dense PK substudy, to enable the conduct of the trial during the COVID-19 pandemic. Additional patients may be enrolled in the dense PK portion of the study to ensure adequate data are captured.	Synopsis: Study Design, Population (Sample Size) Section 3.3 Risk-Benefit Section 9.1.1.1 Footnotes for the Schedule of Events for the Study (#19) Section 6.1 Study Description and Duration Section 7.1 Number of Patients Planned Section 8.4 Method of Treatment Assignment Section 9.1.2 Table 2 Schedule of Events (Dense PK Substudy) Section 9.1.2.1 Footnotes for the Schedule of Events for the Dense PK Substudy (#1, #2, #4, #6)
Additional criterion for pro re nata (PRN) treatment, to allow for patients experiencing substantial disease worsening to receive treatment.	Section 6.1 Study Description and Duration
Minor correction of typographical errors.	Throughout

Amendment 1

The primary purpose of this amendment is to update the inclusion criteria to include patients with better baseline visual acuity to better align with clinical practice patterns.

Change and Rationale for Change	Sections Changed
Name of Compound corrected to High Dose Aflibercept; Medical/Study Director updated	Title Page

Change and Rationale for Change	Sections Changed
Update of pharmacokinetic (PK) data relevant for the indication in the rationale for dose selection and removal of external references	Section 3.2.2 Rationale for Dose Selection
Inclusion criteria updated to include patients with best corrected visual acuity (BCVA) between 24 and 78 letters to better align with clinical practice patterns.	Section 7.2.1 Inclusion Criteria (#2)
Minor additions to the exclusion criteria regarding participation in an investigational study	Section 7.2.2 Exclusion Criteria (#28, #29, #30, #31, #32; new)
Inclusion in Schedule of Events of review of concomitant medications at Screening visit 2; clarification to footnotes to align with table regarding timing of research sample collection at Baseline visit 3; and provision for additional post-dose intraocular pressure (IOP) measurement(s) on day 1 for patients in the dense PK substudy as safety measures	Section 9.1.1 Table 1 Schedule of Events Section 9.1.1.1 Footnotes for the Schedule of Events for the Study (#4, #21) Section 9.1.2 Table 2 Schedule of Events (Dense PK Substudy) Section 9.1.2.1 Footnotes for the Schedule of Events for the Dense PK Substudy (#3, #4; new) Section 9.2.2.1 Intraocular Pressure
Addition of time windows for day 1 sample collection in the dense PK substudy to facilitate patient follow-up	Section 9.1.2 Table 2 Schedule of Events (Dense PK Substudy)
Clarification of timing of collection of adverse events (AE) to align across studies in the development program for high dose (HD) aflibercept	Section 10.1.1 Safety Evaluation, General Guidelines
Minor edits and formatting changes	Throughout

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AOBP	Automated office blood pressure
APTC	Anti-Platelet Trialists' Collaboration
AST	Aspartate aminotransferase
ATE	Arterial thromboembolic event
BCVA	Best Corrected Visual Acuity
BP	Blood pressure
BUN	Blood urea nitrogen
CNV	Choroidal neovascularization
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic)
CRT	Central retinal thickness
DME	Diabetic macular edema
DR	Diabetic retinopathy
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full analysis set
FP	Fundus photography
GCP	Good Clinical Practice
HD	High-dose aflibercept injection
HDL	High-density lipoprotein
IAI	Intravitreal Aflibercept Injection
ICF	Informed consent form
ICH	International Council for Harmonisation
IOP	Intraocular pressure
IRB	Institutional Review Board
IRF	Intraretinal fluid
IV	Intravenous
IVT	Intravitreal
IWRS	Interactive web response system

LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
nAMD	Neovascular “wet” age-related macular degeneration
OCT	Optical coherence tomography
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
PRN	Pro re nata
PT	Preferred term
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RPE	Sub-retinal pigment epithelium
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SD-OCT	Spectral domain optical coherence tomography
SOC	System organ class
SRF	Subretinal fluid
TEAE	Treatment-emergent adverse event
UPCR	Urine protein:creatinine ratio
VEGF	Vascular endothelial growth factor
WBC	White blood cell

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Single-Masked, Active-Controlled Phase 2 Study of the Safety, Tolerability, and Efficacy of Repeated Doses of High-Dose Aflibercept in Patients with Neovascular Age-Related Macular Degeneration
Site Locations	Approximately 60 sites in the United States
Principal Investigator	To be determined
Objectives	The primary objectives of the study are: • To determine the safety of high-dose aflibercept (hereafter referred to as HD) • To determine if HD provides greater intraocular pharmacodynamic (PD) effect and/or longer duration of action compared to 2 mg intravitreal aflibercept injection (IAI, hereafter referred to as IAI) There are no secondary objectives.
Study Design	This is a phase 2, multi-center, randomized, single-masked study in patients with neovascular (wet) age-related macular degeneration (nAMD) that will investigate the efficacy, safety, and tolerability of HD versus IAI. The study consists of a screening/baseline period, a treatment period, and an end of study (EOS) visit at week 44. Patients will be seen monthly through week 44. A total of approximately 100 eligible patients will be randomized into 2 groups in a 1:1 ratio. One group will receive IAI and the other will receive HD. The investigational product will be administered intravitreally (IVT) monthly for 3 initial injections (baseline, week 4, and week 8), followed by additional doses at weeks 20 and 32. At weeks 24, 28, 36 and 40 patients will be evaluated and given a dose (at their randomized dose level) if defined retreatment criteria are met. The study also includes a pharmacokinetic (PK) substudy, with dense blood sampling (dense PK substudy) for systemic drug concentrations and PK assessments for approximately 15 patients from each group from selected sites. Blood pressure measurements will also be taken in these patients on the same days as for the PK sampling. Additional patients (up to approximately 50% more in each treatment group) may be enrolled in the dense PK substudy to ensure adequate data are captured. The primary safety analysis will take place at week 4. The primary efficacy analysis will take place at week 16, with the exploratory endpoints evaluated at week 16 and week 44.
Study Duration	The duration of the study for a patient is approximately 44 weeks, excluding the screening period.

End of Study Definition	The end of study is defined as the last visit of the last patient.
Population	
Sample Size:	The study will enroll approximately 100 patients, to be randomized in a 1:1 ratio. Additional patients may be enrolled in the dense PK portion of the study (up to approximately 50% more in each treatment group) to ensure adequate data are captured.
Target Population:	The study population consists of treatment-naïve patients with nAMD
Treatment(s)	
Study Drug	The HD will be provided as a liquid formulation in a vial. The target concentration of aflibercept is 114.3 mg/mL. The dose will be delivered in an injection volume of 70 µl.
Dose/Route/Schedule:	The IAI will be provided as a liquid formulation in a vial. The target concentration of aflibercept is 40 mg/mL. The dose will be delivered in an injection volume of 50 µl.
Endpoints	
Co-Primary:	The co-primary endpoints are: • Safety, which will be evaluated by assessment of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) through week 4 • The proportion of patients without retinal fluid in the center subfield at week 16
Secondary:	There are no secondary endpoints in this study.
Procedures and Assessments	The efficacy procedures/assessments include: slit lamp exam, indirect ophthalmoscopy, spectral domain optical coherence tomography, fundus photography and fluorescein angiography, evaluation of retinal characteristics, and Best Corrected Visual Acuity (BCVA). The safety procedures/assessments include: ophthalmic examinations, intraocular pressure, assessment of adverse events (AEs), physical examination, vital signs, electrocardiogram, and clinical laboratories. The study also includes pharmacokinetic analyses and potential analysis such as pharmacogenomics, biomarkers, and anti-drug antibodies.
Statistical Plan	<u>Statistical Hypothesis:</u> No formal hypothesis has been defined for the safety analysis at week 4. However, this study will examine the following hypothesis for the superiority testing of the primary efficacy variable: proportion of patients without retinal fluid at week 16. Statistical testing will be conducted to show superiority of HD versus IAI.

H0: p1 = p2, against Ha: p1 ≠ p2

where p_1 and p_2 are the proportion of patients without retinal fluid at week 16 in HD versus IAI, respectively.

Justification of Sample Size:

For this phase 2 safety study, 50 patients per group is sufficient to provide substantial information regarding safety. Assume that the proportion of patients without fluid in the center subfield in the IAI group is 50% with normal approximation and drop out rate is 8%. Then a total sample size of 100 patients will allow estimation of the true treatment difference to be between (+6.7% to +43.3%) at 95% confidence level, if the observed treatment difference is +25% (i.e., observed proportion of patients without fluid in the center subfield in HD group is 75%).

The sample size was estimated based on normal approximation for the confidence interval of the difference in proportions using the commercial software nQuery nTerm 7.0.

Statistical Methods:

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Efficacy Analyses:

Analysis of the primary efficacy variable will take place at week 16. The efficacy analysis for the primary efficacy endpoint will be the comparison between the IAI group and the HD group for the proportion of patients without fluid in the center subfield at week 16. The statistical analysis will be performed using the chi-square test at the 2-sided 5% significance level.

For the primary analysis, missing post-baseline values for a given patient will be imputed using the last observation carry forward (LOCF) procedure to determine the patient's primary efficacy response.

Observed case (OC) analysis will be performed for primary efficacy endpoint as sensitivity analysis, ie, only observed values will be used for analysis.

1. INTRODUCTION

Neovascular (wet) AMD (nAMD) is a major health issue in aging populations globally. Vision loss in nAMD results from the abnormal growth and leakage of blood vessels in the macula. In elderly patients affected by nAMD, vision loss frequently has an even greater impact, as it substantially reduces the visual compensation of functional impairment by other age-related comorbidities, such as arthritis and osteoporosis.

Intravitreally (IVT) administered anti-vascular endothelial growth factor (VEGF) therapies like EYLEA® inhibit neovascular vessel growth and leakage in the retina, and they are currently the standard of care for patients with nAMD. They not only maintain visual function but also provide clinically meaningful visual gains. Treatment of nAMD is chronic and life-long in most patients to suppress retinal edema and recurrences of choroidal neovascularization (CNV). Although the currently approved IVT anti-VEGF therapies are efficacious and well-tolerated, the need for IVT injections every 4 to 8 weeks, specifically in the initial phase and during maintenance of treatment, represents a significant burden to physicians, patients, and caregivers. While the procedure is straightforward and relatively easy to perform, capacity issues for ensuring an appropriate injection frequency in order to achieve patient outcomes similar to those seen in the pivotal studies represent an increasing challenge to individual practices and the healthcare system, overall.

While the efficacy and safety of currently approved anti-VEGF therapies have been established for the treatment of nAMD, there remains an unmet medical need for the development of therapies with the potential to reduce treatment burden while providing at least similar or even improved visual outcomes over currently available standard of care.

Increasing the molar fraction of anti-VEGF therapeutic protein in the dosing formulation is a potential way to bring further benefits to patients with chorioretinal vascular diseases, including nAMD. A higher dose of aflibercept administered IVT has the potential to prolong the drug's therapeutic effects. The resulting extension of treatment intervals early after the initiation of treatment to every 12 weeks or 16 weeks would reduce the number of injections in the first treatment year. A potential decrease in injection-related treatment burden and safety events with fewer injections could be a significant contribution to patient care and healthcare services.

Studies will investigate the safety and efficacy of a high-dose aflibercept IVT injection with the intent of extending the dosing interval, with at least similar functional and potentially improved anatomic outcomes. EYLEA (2 mg dose, administered at a concentration of 40 mg/mL, also called intravitreal aflibercept injection [IAI]) is currently approved in the United States (US) for the treatment of nAMD, and is also approved for the treatment of macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy (DR).

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of the study are:

- To determine the safety of high-dose aflibercept (hereafter referred to as HD).

- To determine if HD provides greater intraocular pharmacodynamic (PD) effect and/or longer duration of action compared 2 mg IAI (hereafter referred to as IAI).

2.2. Secondary Objectives

There are no secondary objectives in this study.

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To generate additional data to determine the effect of HD vs IAI on anatomical measures of response and on visual acuity.
- To characterize the concentrations in plasma over time and corresponding pharmacokinetic (PK) parameters for free, bound, and adjusted bound aflibercept (collectively referred to as bound) and to conduct exploratory PK/PD and/or dose/PD analyses on selected systemic and ocular response variables.
- To study molecular drivers of nAMD or related diseases, the mechanism of action of EYLEA (aflibercept) and the VEGF pathway.

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

A higher dose of aflibercept will extend the interval between doses and/or improve anatomic outcomes with comparable efficacy and safety compared to those of the 2 mg dose of aflibercept.

3.2. Rationale

3.2.1. Rationale for Study Design

Although many patients benefit from treatment with currently available anti-VEGF agents, some patients still need frequent injections, and long-term data suggest that in some patients, visual benefits may be lost if regular dosing, as frequently as every 4 to 8 weeks, is not maintained. Additionally, the treatment paradigm most physicians employ for patients with nAMD after the initial dosing period is "treat and extend", which relies primarily on anatomic assessment as a pharmacodynamic endpoint to determine a dosing interval for individual patients that is thought to optimize benefit/risk and treatment burden. A therapy that can improve and sustain anatomic outcomes with similar safety has the potential to optimize treatment by improving benefit and decreasing treatment burden for patients and physicians.

Increasing the concentration of aflibercept allows a greater amount of drug to be delivered IVT and thus has the potential to increase aflibercept's pharmacological duration of action, and thereby provide additional benefit to patients with this disease. This creates the potential for greater efficacy and may reduce the overall number of injections by extending the treatment interval, thereby reducing burden on both patients and physicians.

This study is designed to investigate the effects of HD versus IAI in patients diagnosed with nAMD.

The goal of the study is to investigate the short-term safety of HD. The study will also investigate the efficacy of HD with the intent of improving anatomic outcomes and potentially extending the dosing interval for HD vs IAI.

3.2.2. Rationale for Dose Selection

Based on considerations of manufacturing capabilities, formulation, stability, and the likelihood of achieving a meaningful extension of the duration of pharmacological effect, an 8 mg IVT dose was selected for evaluation in the present study. In a nonclinical rabbit model of chronic retinal neovascularization and vascular leak, dose-dependent duration of leak suppression was observed after single IVT doses equivalent of up to 8 mg in humans. Pharmacokinetic simulations of free aflibercept concentration-time profiles in human vitreous using a 1-compartment ocular model predicted that the concentration at the end of an 8-week dosing interval for a 2 mg IVT dose would be achieved 18 days later for an 8 mg IVT dose. The present study will evaluate whether an 8 mg IVT dose can extend the dosing interval in the maintenance phase from 8 to 12 weeks or longer.

Studies with intravenous (IV) aflibercept indicated that blood pressure (BP) increase was the earliest PD indicator of systemic effect. Two studies (PDY6655 and PDY6656) evaluated the effects of IV and subcutaneous aflibercept on BP via 24-hour ambulatory BP monitoring in healthy subjects. At the lowest IV dose tested in these studies (1 mg/kg; PDY6656), a maximal increase of approximately 5 mmHg in 24-hour mean change from baseline in systolic BP (SBP) occurred by day 6 after a single dose, SBP returning to baseline by approximately 30 days post-dose.

Assuming linear PK and extrapolating C_{max} and AUC_{last} values (for both mean and maximum individual patient values) from 2 mg IVT, estimated free aflibercept systemic C_{max} and AUC_{last} for an 8 mg IVT dose are approximately 84-236x and 34-136x lower, respectively, than the corresponding values associated with a 1 mg/kg IV dose. Although systemic concentrations of free aflibercept at these IVT doses are appreciably lower than those required to saturate the target mediated elimination pathway, linear extrapolation may overestimate the exposure margins for an 8 mg IVT dose. A threshold dose and/or concentration of free aflibercept associated with BP increase has not yet been determined.

In phase 1 and 2 clinical trials, doses up to 4 mg per eye in monthly intervals, with injection volumes up to 100 µl, were generally well tolerated in patients with both DME and nAMD. In a small number of patients with nAMD, isolated cases of unintentional dosing with 8 mg per eye occurred and were also well tolerated. It is expected that an 8 mg IVT dose will extend the dosing interval relative to 2 mg IVT, thereby reducing the number of injections needed for successful treatment. Hence, with the expectation of both a longer dosing interval resulting in a lower annualized number of injections, and similar safety profile, the 8 mg dose was selected for evaluation in this study.

3.3. Risk-Benefit

Benefits of Treatment with HD:

Nonclinical pharmacology evidence and additional clinical data suggest that an increased molar dose could extend the duration of pharmacological effect of IAI. This would, in turn, reduce the overall treatment burden on patients by increasing the dosing interval after the initial monthly doses, while maintaining or improving the overall risk/benefit profile.

High-dose aflibercept may provide improved patient benefit through:

- longer treatment intervals (≥ every 12 weeks for most patients after initial monthly dosing)
- the potential for improved functional and anatomic efficacy
- less injection-related risk over time
- increased compliance due to reduced treatment burden on patients, caregivers, physicians, and healthcare systems

Risks and Risk Management of Treatment with HD:

The safety profile of HD is considered to be similar to that of IAI, and includes identified risks such as intraocular inflammation/infection, retinal tear, retinal detachment, transient increase in intraocular pressure (IOP), traumatic cataract, and hypersensitivity.

Pharmacokinetic and clinical safety data of IAI have indicated that the known potential risks from systemic administration of anti-VEGF treatments in oncology indications were not identified with local treatment with IAI. Studies performed with IV administration of aflibercept demonstrated that increases in BP were the earliest PD indicator of systemic effects. Estimated exposure margins for free aflibercept after an 8 mg IVT dose, derived from linear extrapolation of available PK data for IVT administered 2 mg IAI, suggest adequate margins relative to those concentrations seen after systemically administered aflibercept associated with an approximate 5 mm Hg mean SBP increase. Robust generation of safety data is planned in this phase 2 trial to evaluate potential systemic exposure-related adverse events (AEs) such as changes in BP and incidence of ocular safety events.

The primary objectives of this study in treatment-naïve nAMD patients are to assess patient safety and to generate important data for pharmacovigilance evaluations. Safety will be assessed by collection of vital signs (including heart rate, BP, and temperature), ocular assessments, AEs, laboratory assessments, and sparse PK sampling. Additionally, the aflibercept PK profile (via dense sampling for drug concentration and PK evaluation) and PD effects (ie, BP changes) will be evaluated in a dense PK substudy.

As risk minimization measures, patients and investigators will be informed about the anticipated safety profile of HD and exclusion criteria will be applied to account for potential safety concerns such as hypersensitivity, pregnancy, ATEs, and uncontrolled arterial hypertension.

Overall Risk-Benefit Balance:

Based on the available preclinical and clinical data, the risk-benefit assessment of HD is considered to be positive and supports the participation of patients with nAMD in the clinical trial program.

COVID-19 Pandemic:

Recognizing that "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the sponsor will only screen patients in this study when the COVID-19 pandemic is controlled such that patients can safely participate in the study. The sponsor will continue initiating study sites for this study, as allowed by local laws and regulations.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoints

The co-primary endpoints are:

- Safety, which will be evaluated by assessment of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) through week 4
- The proportion of patients without retinal fluid in the center subfield at week 16

4.1.2. Secondary Endpoints

There are no secondary endpoints in this study.

4.1.3. Exploratory Endpoints

The exploratory endpoints are:

- The proportion of patients without retinal fluid in the center subfield at week 44
- Change in central retinal thickness (CRT) from baseline through week 16 and week 44
- The proportion of patients without intraretinal fluid (IRF) at week 16 and week 44
- The proportion of patients without subretinal fluid (SRF) at week 16 and week 44
- The proportion of patients without sub-retinal pigment epithelium (RPE) fluid at week 16 and week 44
- The proportion of patients able to maintain dry retina (total fluid, IRF, and/or SRF) through week 16 and week 44
- The proportion of patients able to maintain a 12-week dosing interval from week 8 through week 44
- Change in CRT between dosing visits from week 8 through week 44
- Change in Best Corrected Visual Acuity (BCVA) from baseline, and proportions of patients gaining and losing vision, through week 16 and week 44
- Change in lesion size and choroidal neovascularization (CNV) size from baseline through week 44

- Other safety outcomes (eg, TEAEs, SAEs, vital signs, clinical laboratory values, and intraocular pressure [IOP]) from baseline through week 16 and week 44
- Systemic PK of free and bound aflibercept assessed from baseline through week 44

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

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

5.2. Efficacy Variables

The efficacy variable relevant to the primary efficacy endpoint is the assessment of retinal fluid.

The efficacy variables relevant to the exploratory endpoints are:

- Assessment of retinal fluid levels (total fluid, IRF, and SRF) and retinal thickness on spectral domain optical coherence tomography (SD-OCT, or just OCT)
- Dosing interval
- Visual acuity
- Lesion size

5.3. Safety Variables

The safety variable relevant to the primary safety endpoint is the proportion of patients with TEAEs and SAEs.

The safety variables relevant to the exploratory endpoints are:

- Ocular exams
- Vital signs
- Clinical laboratory values
- IOP

5.4. Pharmacokinetic Variables

The PK variables are the concentrations of free and bound aflibercept in plasma and time, using both sparse sampling (Table 1) and dense sampling (Table 1 and Table 2).

6. STUDY DESIGN

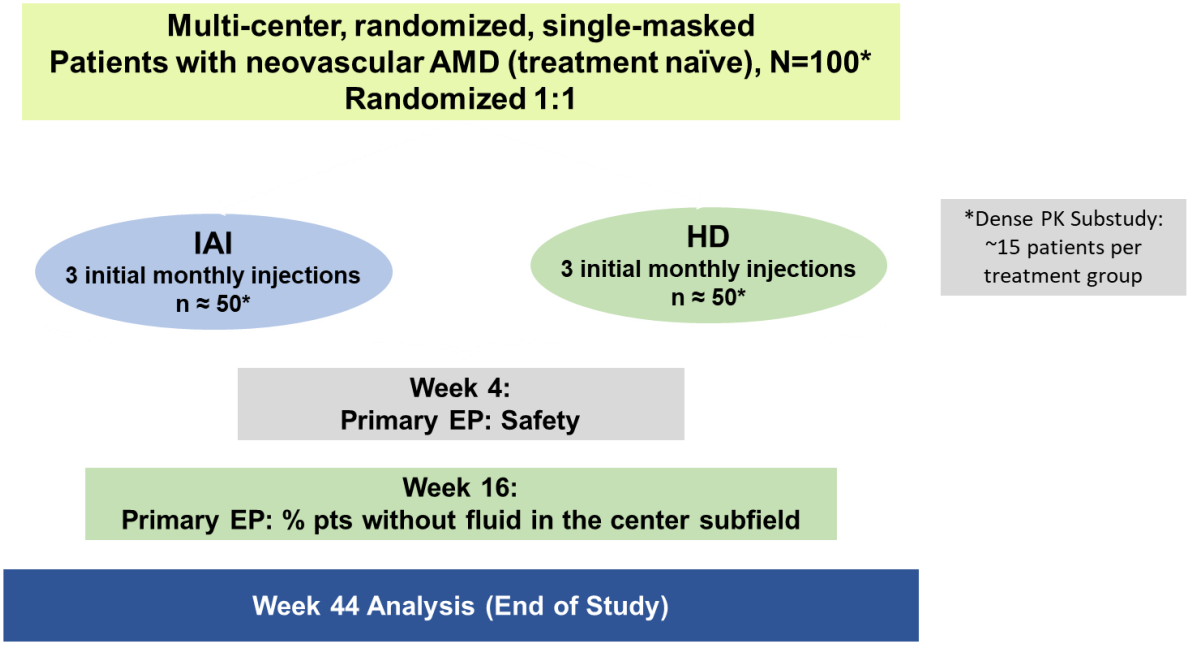
6.1. Study Description and Duration

This phase 2, multi-center, randomized, single-masked study in patients with nAMD will investigate the efficacy, safety, and tolerability of HD versus IAI.

The study consists of a screening/baseline period, a treatment period, and an end of study (EOS) visit at week 44 (Figure 1) (Figure 2). Patients will be seen monthly through week 44. A total of approximately 100 eligible patients will be randomized into 2 groups in a 1:1 ratio. Additional patients may be enrolled in the dense PK substudy (up to approximately 50% more in each treatment group in the dense PK substudy) to ensure adequate data are captured. One group will receive IAI and the other will receive HD. The investigational product will be administered intravitreally (IVT) monthly for 3 initial injections (baseline, week 4, and week 8), followed by additional doses at weeks 20 and 32. At weeks 24, 28, 36 and 40, patients will be evaluated and given a dose (at their randomized dose level) if EITHER of the following criteria are met (PRN criteria):

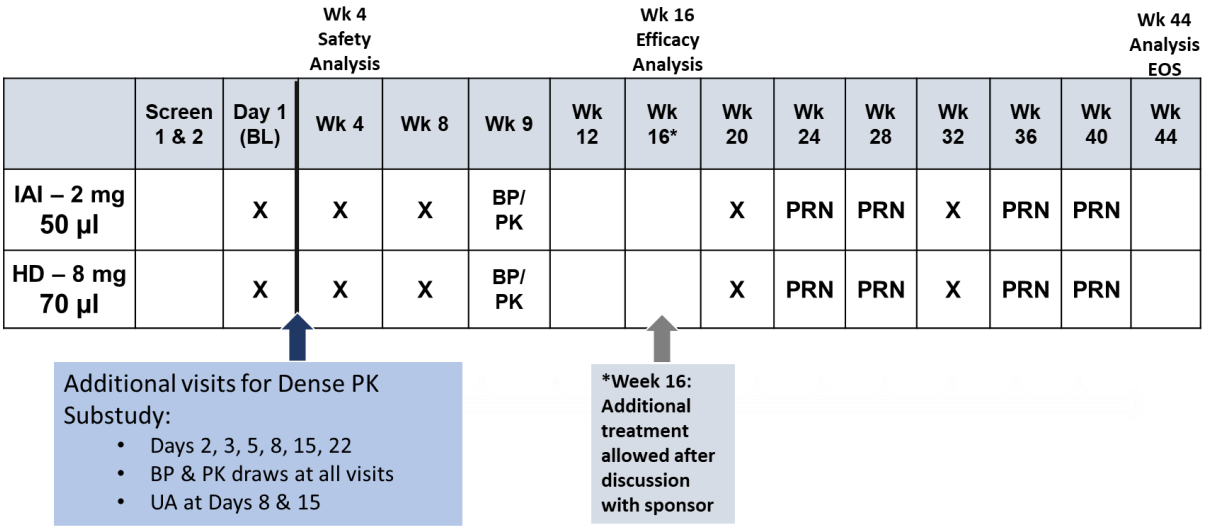
- Loss of ≥5 letters from week 20 BCVA due to disease progression OR
- Anatomical findings that are considered vision-threatening, such as worsening or persistent retinal fluid, new or worsening retinal pigment epithelial detachment (PED), new or persistent hemorrhage, etc.

Figure 1: Study Flow Diagram



EP=endpoint, pts=patients

Figure 2: Dosing Schedule



The primary safety analysis will take place at week 4. The primary efficacy analysis will take place at week 16, with the exploratory endpoints evaluated at week 16 and week 44.

Safety will be assessed by collection of vital signs (including heart rate, BP and, temperature), AEs, and clinical laboratory assessments. All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®).

In all patients, blood samples for measurement of drug concentrations will be obtained prior to the first treatment and at prespecified time points throughout the course of the study. In addition, a DNA sample will be collected from those who sign the informed consent form (ICF) for the genomic substudy.

Dense PK Substudy:

Approximately 15 patients from each group from selected sites will be chosen for a dense PK substudy (Table 2). Additional patients (up to approximately 50% more in each treatment group in the dense PK substudy) may be enrolled to ensure adequate data are captured. Blood pressure measurements will also be taken in these patients on the same days as for the PK sampling. This may be done at the clinical study site, or on certain visits, by the site personnel or another healthcare professional at a remote location (eg, the patient's home or another appropriate location; See Section 9.1.2 , Table 2).

6.1.1. End of Study Definition

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

6.2. Planned Interim Analysis

No formal interim analyses will be performed. However, data may be reviewed in this single-masked study at various time points for safety and/or efficacy.

6.3. Study Committees

6.3.1. Adjudication Committee

Potential arterial thromboembolic events (ATEs) will be evaluated by a masked adjudication committee, according to criteria formerly applied and published by the Anti-Platelet Trialists' Collaboration (APTC) (Antithrombotic Trialists' Collaboration, 1994) (Antithrombotic Trialists' Collaboration, 2002). An ATE is defined as a nonfatal myocardial infarction (MI), nonfatal ischemic stroke, nonfatal hemorrhagic stroke, or death resulting from vascular or unknown causes. The committee will include 2 to 3 cardiologist-equivalent adjudicators, and the activities of the committee will be governed by a charter.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

The study will enroll approximately 100 patients, to be randomized in a 1:1 ratio. Additional patients may be enrolled in the dense PK portion of the study (up to approximately 50% more in each dense PK treatment group) to ensure adequate data are captured.

7.2. Study Population

The study population consists of treatment-naïve patients with nAMD.

7.2.1. Inclusion Criteria

A patient must meet the following criteria at both the screening and/or the randomization visits to be eligible for inclusion in the study:

1. Men or women ≥50 years of age with active subfoveal CNV secondary to nAMD, including juxtafoveal lesions that affect the fovea in the study eye as assessed by an independent reading center
2. Best Corrected Visual Acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 78 to 24 (Snellen equivalent of 20/32 to 20/320) in the study eye
3. Willing and able to comply with clinic visits and study-related procedures
4. Provide informed consent signed by study patient or legally acceptable representative

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria at either the screening or randomization visits will be excluded from the study:

1. Evidence of CNV due to any cause other than nAMD in either eye
2. Subretinal hemorrhage in the study eye that is ≥50% of the total lesion area

3. Evidence of DME or diabetic retinopathy (defined as more than 1 microaneurysm) in either eye in diabetic patients
4. Prior use of IVT anti-VEGF agents (aflibercept, ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) in the study eye
5. Prior IVT investigational agents in either eye (eg, anti-ang-2/anti-VEGF bispecific monoclonal antibodies, gene therapy)
6. Previous use of intraocular or periocular corticosteroids within 120 days of screening or treatment with an IVT steroid implant at any time in the study eye
7. Treatment with ocriplasmin in the study eye at any time
8. Yttrium-aluminium-garnet capsulotomy in the study eye within 14 days of the screening visits
9. History of vitreoretinal surgery (including scleral buckling) in the study eye
10. Intraocular pressure ≥25 mm Hg in the study eye
11. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye
12. Any intraocular inflammation/infection in either eye within 90 days of the screening visit
13. Any history of macular hole of stage 2 and above in the study eye
14. Current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in the study eye
15. 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)
16. Ocular conditions with poorer prognosis in the fellow eye
17. Inability to obtain fundus photographs, fluorescein angiography (FA), or OCT (eg, due to media opacity, allergy to fluorescein dye or lack of venous access) in the study eye
18. Any prior systemic anti-VEGF administration
19. Uncontrolled diabetes mellitus in the opinion of the investigator
20. Uncontrolled BP (defined as systolic >140 mm Hg or diastolic >90 mm Hg). Patients may be treated with up to 3 agents known to have anti-hypertensive effects for arterial hypertension to achieve adequate BP control. This limit applies to drugs that could be used to treat hypertension even if their primary indication in the patient was not for BP control. Any recent changes in medications known to affect BP need to be stable for 90 days prior to the screening visit.
21. Variation by more than 10% in the 3 pre-randomization BP measures recorded at the screening 1, screening 2, and randomization visits
22. History of cerebrovascular accident/ transient ischemic attack or myocardial infarction/ acute coronary syndrome within 180 days of screening visit
23. Renal failure, dialysis, or history of renal transplant

24. Known sensitivity to any of the compounds of the study formulation
25. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor
26. Pregnant or breastfeeding women
27. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 90 days after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    c. bilateral tubal ligation
    d. vasectomized partner
    e. and or sexual abstinence†, ‡

*Postmenopausal women must be amenorrhoeic 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.

†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.

‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

28. Participation in an investigational study within 30 days prior to screening visit that involved treatment with any drug (excluding vitamins and minerals) or device
29. Any other intraocular surgery within 12 weeks (84 days) before the screening visit (see Exclusion Criterion #9)
30. History of corneal transplant or corneal dystrophy in study eye
31. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of IVT injections, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety
32. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications
33. Any active, unresolved systemic infectious disease that, in the opinion of the investigator, would interfere with the patient's ability to complete the study. NOTE: A patient who has a documented, positive PCR or serology test for SARS-CoV-2 may be enrolled provided the patient has:

1) Recovered from COVID-19 (all COVID-19-related symptoms and major clinical findings which can potentially affect the safety of the patient should be resolved to baseline), and

2) Had 2 negative results from a health authority-authorized nucleic acid amplification (PCR) test for COVID-19 taken at least 48 hours apart.

7.2.3. Additional Exclusion Criteria for the Dense PK Substudy

1. Prior IAI in the fellow eye
2. Patients on more than 2 anti-hypertensive medications
3. Patients with known cardiac arrhythmia
4. Patients who, in the opinion of the investigator, are unlikely to have stable BP over the course of the study (eg, due to known non-compliance with medication)

7.3. 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/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.3.

Rules for discontinuation of study treatment are discussed in Section 8.3.2.

7.4. Replacement of Patients

Patients prematurely discontinued from study will not be replaced. However, if a patient from the dense PK substudy discontinues before providing the PK sample at visit 7, an additional patient may be enrolled in the dense PK substudy.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

The HD will be provided as a liquid formulation in a vial. The target concentration of aflibercept is 114.3 mg/mL. The dose will be delivered in an injection volume of 70 µl.

The IAI will be provided as a liquid formulation in a vial. The target concentration of aflibercept is 40 mg/mL. The dose will be delivered in an injection volume of 50 µl.

Instructions on dose preparation are provided in the pharmacy manual.

8.2. Additional Treatment

Deviation from the treatment schedule defined in the protocol is discouraged. Efforts should be made to ensure adherence to the protocol-specified dosing intervals. If, however, in the investigator's judgement, a 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 at week 16. The investigator must make reasonable efforts to consult with the study director or sponsor designee prior to additional treatment being allowed. Patients will receive their randomized dose of aflibercept if it is determined that additional treatment will be administered.

Patients who receive additional treatment will continue to receive their randomized treatment at future visits and will remain masked to treatment assignment. Data from patients receiving additional treatment will be censored from the time additional treatment is administered. Reasons for the decision to give additional treatment will be captured in the CRF.

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

8.3.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and 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 permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.3.

8.4. Method of Treatment Assignment

Approximately 100 patients will be randomized in a 1:1 ratio to receive either IAI or HD according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Additional patients may be enrolled in the dense PK portion of the study (up to approximately 50% more in each treatment group) to ensure adequate data are captured.

8.5. Masking

This is a single-masked study. The patients, visual acuity examiners, and reading center will be masked to treatment assignment.

8.6. Treatment Logistics and Accountability

8.6.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC 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 destroyed / returned to the sponsor or designee.

8.6.3. Treatment Accountability

All drug accountability records must be kept current.

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

- dispensed to each patient
- 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.

8.6.4. Treatment Compliance

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

8.7. Concomitant Medications

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

If a pretreatment concomitant medication is administered in the study eye before injection (eg, antibiotic or anesthetic), it must be administered for fellow eye treatment as well.

8.7.1. Prohibited Medications

Introduction of new anti-hypertensive medications or changes to current regimens for the management of chronic hypertension are not anticipated during the course of the study, and any changes in regimen must be captured in the electronic data capture (EDC). If a patient reports new or increased use of anti-hypertensive medications, the principal investigator (PI) should discuss with the patient's provider whether or not investigational treatment should be discontinued.

Study Eye:

Patients are not allowed to receive any standard or investigational treatment for nAMD in the study eye other than their assigned study treatment with HD or IAI, as specified in the protocol. This includes medications administered locally (eg, IVT, topical, juxtascleral, or periorbital routes), as

well as those administered systemically, with the intent of treating nAMD in the study eye or fellow eye.

Fellow Eye:

If the fellow eye has nAMD, or any other approved indication, IAI (2 mg) will be allowed and supplied through the IWRS. Patients are not allowed to receive any other anti-VEGF agent in the fellow eye.

Patients enrolled in the dense PK substudy cannot receive IAI (2 mg) in the fellow eye before week 12.

Non-Ocular (Systemic):

Non-ocular (systemic) standard or investigational treatments for nAMD of the study or fellow eye are not permitted. Systemic anti-angiogenic agents and anti-Ang2 inhibitors are not permitted during the study.

8.7.2. 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, are allowed.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19, are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

9.1. Schedule of Events

9.1.1. Schedule of Events for the Study

The study assessments and procedures for the study are presented by study period and visit in Table 1.

Table 1: Schedule of Events

Study Procedure	Screening Visit 1	Screening Visit 2	Baseline Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	EOS Visit 15
Month			0	1	2	-	3	4	5	6	7	8	9	10	11
Week			0	4	8	~9	12	16	20	24	28	32	36	40	44
Day	-21 to -1	-20 to -1	1	29	57	61	85	113	141	169	197	225	253	281	309
Window (day)				±5[1]	±5[1]	±2	±5[2]	±5[2]	±5[2]	±5[2]	±5	±5[2]	±5	±5	±5[2]
Screening/Baseline:															
Informed consent	X														
Dense PK sampling informed consent[3]	X														
Genomic substudy/ FBR substudy informed consent form [4]	X														
Inclusion/Exclusion	X		X												
Medical history	X														
Demographics	X														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X												
Administer Study Drug[5]															
Study drug			X	X	X				X	X PRN[6]	X PRN[6]	X	X PRN[6]	X PRN[6]	
Ocular Efficacy and Safety (bilateral unless indicated):															
Refraction and BCVA (ETDRS)[7]	X		X	X	X		X	X	X	X	X	X	X	X	X
IOP[8]	X		X	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	X	X
Indirect ophthalmoscopy[9]	X		X	X	X		X	X	X	X	X	X	X	X	X
FA, FP[10]	X						X		X						X
SD-OCT[10]	X		X	X	X		X	X	X	X	X	X	X	X	X
Non-ocular Safety:															
Physical examination	X														
Vital signs[11, 12, 13]	X	X[14]	X	X	X	X[14]	X	X	X	X	X	X	X	X	X
ECG	X														X
Adverse events	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[15]:															
Hematology	X						X								X

Study Procedure	**Screening Visit 1**	**Screening Visit 2**	**Baseline Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**EOS Visit 15**
Month			0	1	2	-	3	4	5	6	7	8	9	10	11
Week			0	4	8	~9	12	16	20	24	28	32	36	40	44
Day	-21 to -1	-20 to -1	1	29	57	61	85	113	141	169	197	225	253	281	309
Blood chemistry	X						X								X
Pregnancy test (women of childbearing potential)[16]	X Serum		X Urine	X Urine	X Urine				X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	
Urinalysis/UPCR[17]	X			X[18]			X								X
Pharmacokinetics and Research Sampling:															
PK samples (dense)[19]			See schedule below	X	X	X	X	X	X	X		X			X
PK samples (sparse)[20]			X		X	X	X			X		X			X
Research sample[21]			X												X
Genomic DNA sample (optional) [4]			X												

BCVA=Best Corrected Visual Acuity, ECG=electrocardiogram, EOS=end of study, ETDRS=Early Treatment Diabetic Retinopathy Study, FA=fluorescein angiography, FBR=future biomedical research, FP=fundus photography, IOP=Intraocular pressure, PK=pharmacokinetics, PRN=pro re nata (as needed), SD-OCT=spectral domain optical coherence tomography, UPCR=urine protein:creatinine ratio

9.1.1.1. Footnotes for the Schedule of Events for the Study

1. For patients in the dense PK substudy, the visit window is ± 0 days.
2. For patients in the dense PK substudy, the visit window is ± 2 days.
3. Signed only by patients participating in the dense PK substudy and in addition to the study ICF.
4. The optional genomic and FBR substudy ICF should be presented to patients at the screening visit and may be signed at any subsequent visit at which the patient chooses to participate after screening. The genomic DNA sample should be collected on day 1/baseline (pre-dose) or at any study visit from patients who have signed the substudy ICF.
5. Refer to pharmacy manual for study drug injection guidelines. Following study drug injection, patients will be observed for approximately 30 minutes.
6. Patients will be dosed as needed per criteria in Section 6.1.
7. Patients enrolled at sites participating in the optional visual function substudy may undergo additional visual function tests. See study procedure manual for details.
8. Intraocular pressure will be measured bilaterally at all study visits. On days when study drug is administered, IOP should also be measured approximately 30 minutes after administration of study drug, in the study eye only. Intraocular pressure will be measured using Goldman applanation tonometry or Tono-pen™ and the same method of measurement must be used in each patient throughout the study.
9. Indirect ophthalmoscopy should be performed bilaterally at all visits. On days when study drug is administered, it should also be performed immediately after administration of study drug (study eye only).
10. The same SD-OCT/FA/FP imaging system used at screening and day 1 must be used at all subsequent visits in each patient. Images will be taken in both eyes before dosing at each required visit.
11. Vital signs (temperature, BP, heart rate) should be measured pre-injection, per the procedure outlined in the study procedure manual. Blood pressure assessments will be taken using automated office blood pressure (AOBP) with the Omron Model HEM 907XL (or comparable). Measures will be taken in triplicate and a mean measure as displayed by the device will be recorded in the EDC. Detailed instructions can be found in the study procedure manual.
12. Timing of BP assessment at all visits must be within 2 hours of planned time of dosing on day 1 for patients in the dense PK substudy. For all other patients, this window should be adhered to as closely as possible.
13. For patients participating in the dense PK substudy, HR and BP also will be collected according to the schedule in Table 2.
14. Only BP and heart rate will be measured at these visits. No temperature measures are required.

15. All samples collected for laboratory assessments should be obtained prior to administration of fluorescein and prior to administration of study drug.
16. For women of childbearing potential, a negative serum pregnancy test at screening is required for eligibility. A negative urine pregnancy test is required before treatment is administered at subsequent visits.
17. For patients participating in the dense PK substudy, urinalysis/UPCR will also be collected according to the schedule in Table 2.
18. Week 4 collection of urinalysis/UPCR only for patients in the dense PK substudy.
19. Dense PK sampling will be performed in approximately 30 patients (15 in each group) drawn according to the schedule in Table 2. On dosing days, BP and PK samples must be collected prior to study drug administration. Additional patients (up to approximately 50% more in each treatment group) may be enrolled in the dense PK substudy to ensure adequate data are captured.
20. Sparse PK sampling will be performed in all patients not enrolled in the dense PK substudy according to the schedule defined in Table 1. On dosing days, BP and PK samples should be collected prior to study drug administration, and the timing of BP and PK sample collection should be within ±2 hours of the time of the injection on day 1 of the study.
21. Exploratory research serum sample should be drawn prior to the administration of study drug at baseline (visit 3, day 1) and week 44.

9.1.2. Schedule of Events for the Dense PK Substudy

The additional study assessments and procedures for the dense PK substudy are presented by study period and visit in Table 2.

Table 2: Schedule of Events (Dense PK Substudy)

Visit	Dose	Assessment Day and Time (h)		Dense PK Sample Collection	Heart Rate and Blood Pressure[1,2]	Urinalysis / UPCR
Visit 3 (Baseline)	X	1	Time of first dose	X (pre-dose)	X	
			4h post-dose (±30 min)[3]	X		
			8h post-dose (±2 h)[4]	X		
		2	±2h[5]	X	X	
		3	±2h[5]	X	X	
		5	±2h[5]	X	X	
		8	±2h[5]	X	X	X[6]
		15	±2h[5]	X	X	X[6]
		22	±2h[5]	X	X	

9.1.2.1. Footnotes for the Schedule of Events for the Dense PK Substudy

1. Timing of all BP assessments must be within ±2 hours of the time of dosing on day 1. This may be done at the clinical study site or by the site personnel or another healthcare professional at a remote location (eg, the patient's home or other appropriate location). Regardless of where BP measurements are taken, the procedure described in Section 9.2.3.1 must be followed.

2. Blood pressure assessments will be taken using automated office blood pressure (AOBP) with the Omron Model HEM 907XL (or comparable). Measures will be taken in triplicate and a mean measure as displayed by the device will be recorded in the EDC. Detailed instructions can be found in the study procedure manual.
3. Intraocular pressure will be measured at approximately 4 hours post-dose only if the IOP measurement from approximately 30 minutes to 60 minutes post-dose remains clinically significantly higher than the pre-injection reading.
4. Intraocular pressure will be measured at approximately 8 hours post-dose only if the IOP measurements from approximately 30 minutes to 60 minutes and approximately 4 hours post-dose remain clinically significantly higher than the pre-injection reading.
5. PK draw for all assessment days are to be performed within ±2 hours to the time of dosing on day 1.
6. This may be done at the clinical study site or by the site personnel or another healthcare professional at a remote location (eg, the patient's home or other appropriate location).

9.1.3. Early Termination Visit

Patients who are withdrawn from the study before the primary efficacy endpoint visit (week 16) will be asked to return to the clinic for 2 additional visits: once for an early termination visit consisting of the end of study (EOS, Visit 15) assessments described in Table 1 and again at the approximate time for visit 8 (week 16/day 113).

9.1.4. 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.

9.2. Study Procedures

9.2.1. 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: medical history, demographics, and physical examination.

9.2.2. Ocular Procedures (Efficacy and Safety)

9.2.2.1. Intraocular Pressure

Intraocular pressure will be measured in both eyes at every visit using Goldmann applanation tonometry or Tono pen™, as specified in Table 1. The same method of IOP measurement must be used throughout the study for each individual patient. On dosing visits, IOP will also be measured approximately 30 minutes post-dose (study eye).

For patients in the dense PK substudy, IOP will also be measured 4 hours post-dose if the reading from approximately 30 minutes to 60 minutes post-dose remains clinically significantly higher

than the pre-dose reading, and again at approximately 8 hours post-dose if the reading from approximately 4 hours post-dose remains clinically significantly higher than the pre-dose reading.

9.2.2.2. Slit Lamp Examination

Patients' anterior eye structure and ocular adnexa will be examined bilaterally pre-dose at each study visit using a slit lamp (see study procedure manual) by the investigator, as specified in Table 1.

9.2.2.3. Indirect Ophthalmoscopy

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, as specified in Table 1. Post-dose evaluation must be performed immediately after injection.

9.2.2.4. Fundus Photography/Fluorescein Angiography

The anatomical state of the retinal vasculature will be evaluated by FP and FA as specified in Table 1. Fundus photography and FA will be captured and transmitted to an independent reading center for both eyes. For FA, the study eye will be the transit eye.

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

9.2.2.5. Spectral Domain Optical Coherence Tomography

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

9.2.2.6. Best Corrected Visual Acuity

Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (Early Treatment Diabetic Retinopathy Study Research Group, 1985) at 4 meters at each study visit, as specified in Table 1. Visual acuity examiners must be certified to ensure consistent measurement of BCVA, and must remain masked to treatment assignment, treatment schedule and study eye. Best corrected visual acuity should be done before any other ocular procedures are performed (see study procedure manual). A detailed protocol for conducting visual acuity testing and refraction can be found in the study procedure manual. Patients enrolled at sites participating in the optional visual function substudy may undergo additional visual function tests. See study procedure manual for details.

9.2.3. Safety Procedures (Non-ocular)

9.2.3.1. Vital Signs

Vital signs, including temperature, BP, and heart rate will be collected pre-dose at designated time points according to Table 1.

For all patients, BP assessments at designated time points (see Table 1 and Table 2) will be taken using automated office blood pressure (AOBP) with the Omron Model HEM 907XL (or comparable). Measures will be taken in triplicate and a mean measure as displayed by the device will be recorded in the EDC. Vital sign measurements will be taken once the patient has been sitting down for a minimum of 5 minutes. Detailed instructions can be found in the study procedure manual.

9.2.3.2. Physical Examination

A physical examination, including height and weight, will be performed at the screening visit 1.

9.2.3.3. Electrocardiogram

A standard 12 lead ECG measurement will be measured at visits specified in Table 1. Heart rate will be recorded from the ventricular rate and the PR, QRS, RR and QT intervals will be recorded. The ECG strips or report will be retained with the source documentation. Electrocardiograms will be forwarded to a central reader.

9.2.3.4. Laboratory Testing

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

Samples for laboratory testing will be collected at time points according to Table 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) + 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

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

Women of childbearing potential must have a documented negative serum pregnancy test before randomization at visit 3. Urine pregnancy tests will be performed prior to any treatment administration (in study eye or fellow eye) at any regular or unscheduled visit.

A negative result must be documented before a dose can be given in the study eye or in the fellow eye.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment 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/Study Director 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 10.1.1.

9.2.4. Drug Concentration and Measurements

Blood samples for drug concentration will be collected at the visits listed in Table 1 and at the time points listed in Table 1 and Table 2 for sparse and dense PK sampling. Instructions for PK blood sample collection will be included in the laboratory manual provided to study sites.

For all patients, a research serum sample will be collected at baseline and week 44 for potential analyses (such as biomarkers or anti-drug antibody assessments).

9.2.5. Future Biomedical Research

Additional analyses may be performed on leftover samples as well as PK samples from patients who consent to participate in the optional future biomedical research substudy. Samples will be banked in long term storage. The leftover samples will be stored for up to 15 years after the final date of the database lock. The leftover samples may be utilized for future biomedical research of nAMD, related diseases or pathways blocked by study treatment, and any adverse reactions that may emerge. These samples may also be used for unrelated assay development and validation purposes. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the clinical study report (CSR).

9.2.5.1. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics substudy will be required to consent to this optional substudy before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (pre-dose), but can be collected at a later study visit. DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of nAMD and related diseases. These samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to nAMD, other nAMD clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of nAMD as well as related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or nAMD and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, and DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection period, from the time of signing the ICF to the end of on-treatment period (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent 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 should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow up on treatment-emergent serious adverse events (SAEs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the Investigator assesses as related to study drug should also be reported.

All SAEs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the study drug. For SAEs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

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

- **SAEs**
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, 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.

10.2. Definitions

10.2.1. 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 (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. 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 a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new AE as determined by the investigator or treating physician
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

An ocular important medical event may include the following:

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

Criteria for reporting SAEs must be followed for these events.

10.2.3. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the patient 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.

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

10.2.4. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical

judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the Study Drug

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the Injection Procedure

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

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

The possible answers are:

Not Related: There is a 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

Causality to the Study Conduct (Protocol-Specified Procedure)

- Related:
  - The AE follows a reasonable temporal sequence from a protocol-specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol-specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient 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/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; 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.

10.4. Notifying Health Authorities, Institutional Review Board, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, Institutional Review Boards (IRBs), and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (aflibercept), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only masked information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB unless delegated to the sponsor.

Event expectedness for study drug (aflibercept) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IRBs as appropriate.

11. 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 first database lock.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

No formal hypothesis has been defined for the safety analysis at week 4.

However, the study will examine the following hypothesis for the superiority testing of the primary efficacy variable: proportion of patients without retinal fluid at week 16. Statistical testing will be conducted to show superiority of HD versus IAI.

H0: $p_1 = p_2$, against Ha: $p_1 \neq p_2$

where p_1 and p_2 are the proportion of patients without retinal fluid at week 16 in HD versus IAI, respectively.

11.2. Justification of Sample Size

For this phase 2 safety study, 50 patients per group is sufficient to provide substantial information regarding safety. Assume that the proportion of patients without fluid in the center subfield in the IAI group is 50% with normal approximation and drop out rate is 8%. Then a total sample size of 100 patients will allow estimation of the true treatment difference to be between (+6.7% to +43.3%) at 95% confidence level, if the observed treatment difference is +25% (ie, observed proportion of patients without fluid in the center subfield in HD group is 75%).

The sample size was estimated based on normal approximation for the confidence interval of the difference in proportions using the commercial software nQuery nTerm 7.0.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients; it is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

11.3.2. 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. Additional safety analyses will be performed on patients included in the dense PK substudy.

11.3.3. Pharmacokinetic Analysis Set

The PK analysis population includes all patients who received any study drug and who had a at least 1 non-missing result following the first dose of study drug. Patients will be analyzed based on actual treatment received.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

11.4.1. Patient Disposition

The following will be provided:

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

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

Analysis of the primary efficacy variable will take place at week 16. The efficacy analysis for the primary efficacy endpoint will be the comparison between the IAI group and the HD group for the proportion of patients without fluid in the center subfield at week 16. The statistical analysis will be performed using the chi-square test at the 2-sided 5% significance level.

For the primary analysis, missing post-baseline values for a given patient will be imputed using the last observation carry forward (LOCF) procedure to determine the patient's primary efficacy response.

Observed case (OC) analysis will be performed for primary efficacy endpoint as sensitivity analysis, ie, only observed values will be used for analysis.

11.4.3.2. Exploratory Efficacy Analysis

For the following categorical exploratory endpoints, analyses will be performed in the same manner as for the primary efficacy analysis:

- The proportion of patients without retinal fluid in the center subfield at week 44
- The proportion of patients without intraretinal fluid (IRF) at week 16 and week 44
- The proportion of patients without subretinal fluid (SRF) at week 16 and week 44
- The proportion of patients without RPE fluid at week 16 and week 44
- The proportion of patients able to maintain dry retina (total fluid, IRF, and/or SRF) through week 16 and week 44
- The proportion of patients able to maintain a 12-week dosing interval from week 8 through week 44

The continuous exploratory endpoints (such as mean change in CRT, mean change in BCVA, mean change in lesion size and CNV size) will be summarized descriptively. They will also be analyzed using an analysis of covariance model with treatment as the main effect and baseline measurement as covariate. Missing data will be imputed using the LOCF method. In addition, supportive analyses may be conducted using mixed-model repeated measures (MMRM) analysis model (of which missing values will not be imputed explicitly) using treatment group, visit and baseline measurements as factors.

11.4.4. Control of Multiplicity

There will be no control for multiplicity.

11.4.5. Safety Analysis

The safety variables will be analyzed on the SAF for the on-treatment period from baseline/day 1 through week 4 (primary analysis) and the end of study (week 44).

11.4.5.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period (to determine TEAEs) is defined as the time from the first dose of study drug to the last dose of study drug plus 30 days, or to the last study visit (week 44), whichever is later.
- The posttreatment period is defined as after the end of the on-treatment period.

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

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (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 10.2.3), presented by SOC and PT
- TEAEs by relationship to treatment (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.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, and BP) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics. Blood pressure will be measured in all patients at the time points indicated in Table 1 and Table 2. Changes in BP will be assessed using a time-weighted average change from baseline at select visits and the mean change from baseline at all visits.

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 for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

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.

11.4.5.3. Treatment Exposure

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

11.4.5.4. Treatment Compliance

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

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

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

Main Study:

The concentrations of free and bound aflibercept over time will be summarized by descriptive statistics for each treatment group. No formal statistical hypothesis testing will be performed.

Dense PK Substudy:

The PK parameters to be determined after the first dose for free and bound aflibercept may include, but are not limited to:

- C_{max}
- C_{max}/Dose
- t_{max}
- t_{last}
- C_{last}
- AUC_{inf}
- AUC_{inf}/Dose
- $t_{1/2}$
- C_{trough}

After repeat dosing in the dense PK substudy, PK parameters to be determined may include, but are not limited to, C_{trough}, time to reach steady-state, and accumulation ratio.

The concentrations of free and bound aflibercept over time and selected PK parameters will be summarized by descriptive statistics by treatment group. This descriptive statistical assessment will include the geometric means and ratios of the geometric means for selected PK parameters, as deemed appropriate. No formal statistical hypothesis testing will be performed.

11.5. Interim Analysis

No formal interim analyses will be performed. However, data may be reviewed in this single-masked study at various time points for safety and/or efficacy.

11.6. 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.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

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 EDC system (Medidata RAVE).

12.1.2. Electronic Systems

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

- IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

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.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook 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 EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

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

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

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

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

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRF that will be provided to the sponsor.

12.4.2. 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 obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period 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 (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

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

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

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, 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. Patients 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

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

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB should be informed as soon as possible

- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

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

A copy of the IRB approval letter with a current list of the IRB members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

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

13.5. Clinical Study Data Transparency

Treatment codes will be disseminated to each investigation site approximately 8 weeks following the final study data base lock. Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. Br Med J 2002; 324:71-86.

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

Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol. 1985 Dec;103(12):1796-806.

20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Single-Masked, Active-Controlled Phase 2 Study of the Safety, Tolerability, and Efficacy of Repeated Doses of High-Dose Aflibercept 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 Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this protocol accurately describes the intended conduct of the study.

Study Title: A Randomized, Single-Masked, Active-Controlled Phase 2 Study of the Safety, Tolerability, and Efficacy of Repeated Doses of High-Dose Aflibercept in Patients with Neovascular Age-Related Macular Degeneration

Protocol Number: VGFTe (HD)-AMD-1905

Protocol Version: VGFTe (HD)-AMD-1905 Amendment 3

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00159203 v1.0

ESig Approval	[redacted]
ESig Approval	[redacted]
ESig Approval	[redacted]
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Signature Page for VV-RIM-00159203 v1.0 Approved