STATISTICAL ANALYSIS PLAN
VERSION: 2.0

Clinical Study Protocol 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
Compound:	Intravitreal Aflibercept Injection
Protocol Number:	VGFTe (HD)-AMD-1905
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	Version 2.0 / 26JUL2021 Original Statistical Analysis Plan / 16JUL2020

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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AOBP	Automated office blood pressure
APTC	Anti-Platelet Trialists' Collaboration
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutically Chemical
AUC	Area under the curve
BCVA	Best Corrected Visual Acuity
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CMH	Cochran-Mantel-Haenszel
CNV	Choroidal neovascularization
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
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
IRF	Intraretinal fluid
IVT	Intravitreal
IWRS	Interactive web response system
LOCF	Last observation carry forward

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LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
nAMD	Neovascular “wet” age-related macular degeneration
OC	Observed case
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
PRN	Pro re nata
PT	Preferred term
RBC	Red blood cell
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
SD-OCT	Spectral domain optical coherence tomography
SI	Standard international
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
WHODD	WHO Drug Dictionary

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1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for VGFTe (HD)-AMD-1905 study.

1.1. Background/Rationale

Neovascular "wet" age-related macular degeneration (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. Anti-VEGF agents not only maintain visual function but can also provide clinically meaningful visual gains. Treatment of nAMD must generally be continued throughout a patient's lifetime in order 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, both 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.

This study 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 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). Multiple indications have also received regulatory approval in countries outside the US.

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1.2. Study Objectives

1.2.1. 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).

1.2.2. Secondary Objectives

There are no secondary objectives in this study.

1.2.3. 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.

1.2.4. Modifications from the Statistical Section in the Final Protocol

Not applicable.

1.2.5. Revision History for SAP Amendments

Version 2.0

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. 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.

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Table 1: Revision History for SAP Amendments

Change	Rationale for Change	Section(s)
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.	2.1 Study Design and Randomization 2.2 Sample Size 4.5 Efficacy Variables 4.6.6 Ocular Safety Variables 5.6 Analysis of Efficacy Variable(s) 7 Interim Analysis 11.4 and 11.5 Process to derive data cut-off date
Added a clarifying note: Note: up to and including week 16, aLOCF and LOCF analysis are identical, and so are aOC and OC.	Clarification needed for the new primary timepoint of analysis.	5.6.1 Analysis of Primary Efficacy Variable(s)
Deleted the following typographical error: "Patients who have received additional treatment'	Typographical error	5.6.1. Analysis of Primary Efficacy Variable(s)

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Change	Rationale for Change	Section(s)
Changed: 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. For any patient who receives additional treatment at week 16, measurements after additional treatment is given will be imputed using the last observation prior to additional treatment. Patients will be considered as non-responders if all post-baseline observations are missing. LOCF procedure has been used in previous ophthalmology studies. Therefore, LOCF method will be used in this HD phase 2 study. To: 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. • LOCF analysis: Missing observations are imputed by the last non-missing post-baseline observation. Patients will be considered as non-responders if all post-baseline observations are missing. For any patient who receives additional treatment at week 16, i.e., rescue, upon discussion with the Sponsor, their measurements at time points past week 16 will be imputed using the last observation prior to additional treatment at week 16. For remaining patients, their observed data at time points past week 16 will be included as usual.	Rationale: The analysis timepoint is week 16, so no "carry forward" of data from week 16 is necessary.	5.6.1. Analysis of Primary Efficacy Variable(s)

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Change	Rationale for Change	Section(s)
Deleted statement: "Observed case (OC) analysis will be performed for primary efficacy endpoint as sensitivity analysis, i.e., only observed values will be used for analysis." As a OC and OC are identical for week 16 timepoint and aOC is being refered to later on in this paragraph.	aOC and OC are identical for week 16 timepoint and aOC is being refered to later on in this paragraph.	5.6.1. Analysis of Primary Efficacy Variable(s)
Deleted statement: "Data will not be imputed for the safety analysis.".	Missing dates imputations are described in this SAP.	5.7 Analysis of Safety Data
Changed: TEAEs by relationship to treatment (related, not related), presented by SOC and PT To: Treatment related TEAEs presented by SOC and PT	We will present TEAEs regardless of relationship, and also, separately, treatment-related TEAEs. "Not related" TEAEs will not be summarized separately.	5.7 Analysis of Safety Data
Changed: In addition, the review of safety and efficacy will occur at the following timepoints: • When all patients in the PK substudy (n=~30) have reached week 4, in order to assess safety in a subpopulation after the initial dose • When all patients in the PK substudy (n=~30) have reached week 12, in order to assess safety and efficacy in a subpopulation of patients after the loading phase • When all patients have reached week 12, in order to assess safety and efficacy in the total population at the end of the loading phase To: In addition, a review of the safety and efficacy data will occur periodically throughout the conduct of the study.	Periodic reviews of safety and efficacy data are being completed more frequently than the specific visit cutoffs described in this section.	7 Interim Analysis

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2. INVESTIGATION PLAN

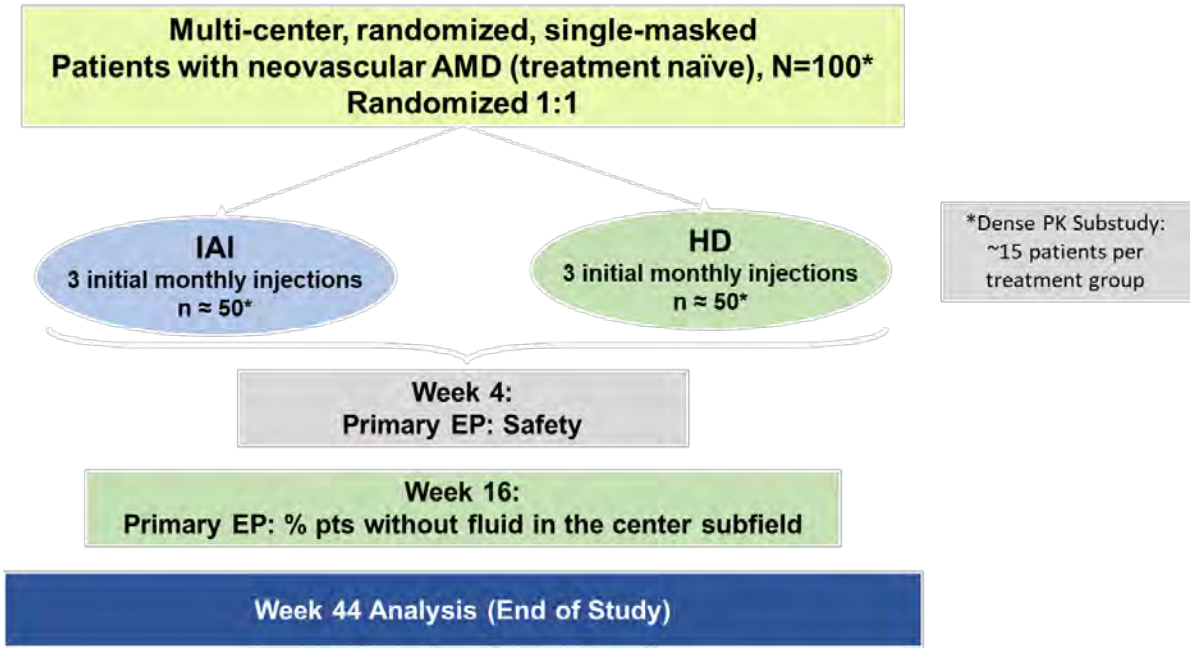
2.1. Study Design and Randomization

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. One group will receive IAI and the other will receive HD. The investigational product will be administered 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 both of the following criteria are met (pro re nata [PRN] criteria):

- Loss of ≥5 letters from week 20 Best Corrected Visual Acuity (BCVA) due to disease progression
- Persistence or recurrence of disease activity indicated by worsening or persistent retinal fluid, or new or persistent hemorrhage

Figure 1: Study Flow Diagram



EP=endpoint, pts=patients

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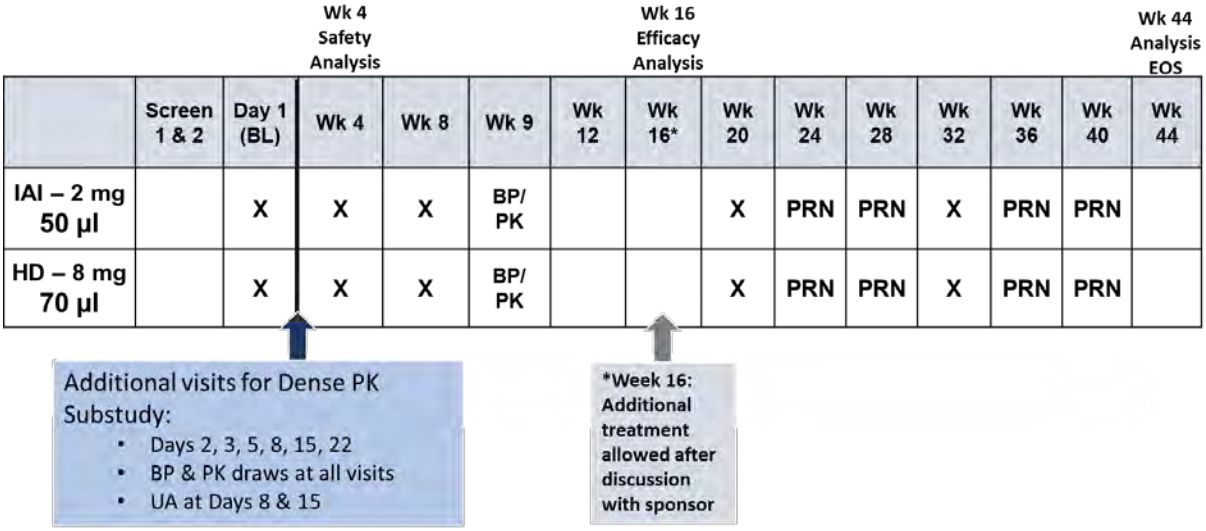
Figure 2: Dosing Schedule



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.

Approximately 100 patients will be recruited and randomized from approximately 60 sites 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). Randomization will be stratified according to whether patients enter into dense PK substudy, to allow for equal allocation in both treatment groups (n~15 patients per group in dense PK substudy).

The Study event table is presented in Appendix 11.1.

Dense PK Substudy

Approximately 15 patients eligible for the dense PK substudy will be randomized to each treatment group. Schedule of study assessments for patients in the PK substudy is given in Table 3 (Section 11.1).

2.2. Sample Size and Power Considerations

For this phase 2 safety study, 50 patients per group are sufficient to provide information regarding safety. Assuming that the proportion of patients without fluid in the center subfield at week 16 in the IAI group is 50% 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 (normal approximation), if the observed treatment difference is +25% (i.e., observed proportion of patients without fluid in the center subfield at week 16 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.

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3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following population of analysis will be used for all statistical analysis:

3.1. Full Analysis Set

The full analysis set (FAS) includes all randomized patients; it is based on the treatment allocated (as randomized).

FAS is the primary analysis set for efficacy endpoints, unless specified otherwise.

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 may be performed on patients included in the dense PK substudy.

3.3. Pharmacokinetic Analysis Set

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

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4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic variables will be summarized:

- Age (year)
- Age category:>=50-<65y; >=65y
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino)
- Baseline Weight
- Baseline Height
- Baseline Body mass index (BMI) calculated from weight and height
- Categorized BMI: BMI<=30 kg/m², BMI >30- <=35 kg/m², BMI >35 kg/m²
- Baseline blood pressure (systolic and diastolic), heart rate, temperature
- Smoking History: Current, Past, Never

The following baseline characteristics will be included:

- BCVA
- Central retinal thickness (CRT)
- Intraocular pressure (IOP)
- CNV size
- Total Lesion Area
- Lesion sub-type

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

4.3. Prior/Concomitant Medication

Medications will be recorded from the time of informed consent to the final study visit. Medications will be coded to the Anatomical Therapeutic Chemical level 2 (ATC, therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

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Mediations will be summarized as follows:

- **Prior medications**: medications started and ended prior to administration of the study drug
- **Concomitant medications**: medications that are ongoing at, or begin after the administration of the study drug
- **New medications**: medications that begin after the start of study treatment

The prior, concomitant and new medication will be summarized by ATC class (ATC level 1) and subclass (ATC level 2).

Variables for concomitant medication description and analysis will include Generic name, ATC level codes, Indication, Dose/Dose Unit, Frequency, Route, start/end date and study day, Duration, Ongoing.

4.4. Treatment Exposure/Compliance

4.4.1. Exposure to Study Drug

The following variables regarding exposure to study drug in the Study Eye for each patient will be summarized:

- The total number of injections administered (including PRN injections and the additional treatment at week 16)
- The total number of injections administered adjusted for additional treatment, that is, including only planned injections for patients who receive additional treatment at week 16, and including planned injections and PRN injections for patients who don't receive additional treatment at week 16
- Proportion of patients who only receive planned injections
- Proportion of patients who receive PRN and the total number of PRN injection administered
- Proportion of patients who receive PRN and the total number of PRN injection administered for patients who do not receive additional treatment at week 16
- Proportion of patients who receive PRN and the total number of PRN injection administered for patients who receive additional treatment at week 16
- Duration of treatment calculated (Weeks) as: [(last study treatment date) - (first study treatment date) + 28]/7 (28 days are added because of the minimum 4 week dosing interval in the study)

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4.4.2. Measurement of Compliance

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

Treatment compliance = (number of received injections through the analysis time)/(number of planned injections during the period of participation in the study through the analysis time) × 100%.Compliance will be summarized as both continuous and categorical variables (<60% vs. >=60%), as well as number of patients receiving 100% injections.

The planned injections above do not include PRN or additional treatment at week 16.

4.5. Efficacy Variables

4.5.1. Primary Efficacy Variable

The proportion of patients without retinal fluid in the center subfield at week 16. Here, without retinal fluid means absence of both IRF and SRF.

4.5.2. Secondary Efficacy Variable

There is no secondary efficacy variable in this study.

4.5.3. Exploratory Efficacy Variables

The exploratory endpoints are:

- The proportion of patients without retinal fluid in the center subfield at week 44
- Change in 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 (absence of IRF and/or SRF) through week 16 and week 44 (Maintain dry is defined as reaching dry and maintaining dry for all subsequent study visits and at least two consecutive visits)
- The proportion of patients able to maintain a 12-week dosing interval from week 8 through week 44, i.e., the proportion of patients who do not receive PRN injections or additional injection at week 16. The denominator is based on the number of patients who complete the study
- Change in CRT between dosing visits from week 8 through week 44 will be summarized in the following intervals:
  - change from week 8 through week 12;
  - change from week 12 through week 16;
  - change from week 16 through week 20;
  - for visit after week 20, change between the dosing visits;

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- Change in BCVA from baseline, and proportions of patients gaining and losing vision, through week 16 and week 44
- Change in lesion size and CNV size from baseline through week 44

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

An Adverse Event (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).

A Serious Adverse Event (SAE) is an AE that is classified as serious according to the criteria specified in the protocol.

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a PT and associated primary SOC according to the MedDRA® (the Version 22.0 or the latest current available version).

Other variables for AE description and analysis will include AE Verbatim Term, AE start date and end date/ongoing and corresponding study day, AE duration, relationship of AE to study drug, relationship of AE to study procedure, seriousness, severity, action due to AE, treatment of AE and outcome.

In addition to standard AE summaries, adjudicated Anti-Platelet Trialists' Collaboration (APTC) events, intraocular inflammation, hypertension and nasal mucosa events will be summarized as described in Section 5.7.1.

4.6.2. Surgeries

All the surgeries after informed consent are collected on the CRF and are coded by MedDRA. Treatment emergent surgery is defined as surgery performed on or after the start of study treatment.

4.6.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, and other.

Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Functions are defined as follows:

- Blood chemistry panel: Sodium, Potassium, Chloride, Carbon dioxide, Calcium, Glucose, Albumin, Total Protein (serum), Creatine, Blood urea nitrogen (BUN), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase, Lactate dehydrogenase (LDH), Total bilirubin, Total cholesterol

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(Low-density lipoprotein [LDL] + high-density lipoprotein [HDL]), Triglycerides, Uric acid, Creatine phosphokinase (CPK)

- Hematology panel: Hemoglobin, Hematocrit, Red blood cells (RBCs), White blood cells (WBCs), Red Cell Indices, Platelet count and Differential count (Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils)
- Urinalysis: Color, Clarity, pH, Specific gravity, Ketones, Protein, Urine protein:creatinine ratio (UPCR), Glucose, Blood, Bilirubin, Leukocyte esterase, Nitrite, WBC, RBC, Hyaline and other casts, Bacteria, Epithelial cells, Crystals, Yeast

4.6.4. Vital Signs

Variables of analysis for vital signs include temperature, blood pressure (BP, systolic and diastolic) and heart rate.

4.6.5. 12-Lead ECG

Variables of 12-Lead Electrocardiogram (ECG) include PR interval, QRS interval, RR interval, QT interval, Ventricular rate and Heart rate.

4.6.6. Ocular Safety Variables

Ocular AEs (including IOI) will be summarized as described in Section 4.6.1 and Section 5.7.1. In addition, other variables of analysis for ocular safety measures include IOP. Variables of analysis in Study Eye from baseline through week 16 and week 44 include proportion of patients with increased IOP:

- ≥ 10 mmHg increase in IOP measurement from baseline to any pre-dose measurement
- > 21 mmHg for any pre-dose measurement
- ≥ 25 mmHg for any pre-dose measurement
- ≥ 35 mmHg at any time

Post dose IOP measurement should be the last IOP recorded.

4.7. Pharmacokinetic Variables

The PK variables are the concentrations of free, bound, adjusted bound, and total aflibercept in plasma at each time point, using both sparse and dense sampling.

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5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum.

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

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined for SAF and FAS. Parameters to be summarized include those described in Section 4.1.

5.2. Medical History

Medical history will be descriptively summarized for FAS. Summaries will show number and percentage of patients by primary SOC and PT. The tables will be sorted by decreasing frequency of primary SOC. Within each primary SOC, PTs will be sorted by decreasing frequency.

5.3. Prior/Concomitant Medications

All prior/concomitant/new medications, dictionary coded by WHODD, will be descriptively summarized by treatment group for SAF. Summaries will present number and percentage of patients for the medication groups described in Section 4.3 for all medications, by decreasing frequency of ATC followed by ATC level 2, ATC level 4 and PT. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication.

When medication start/end date is missing, the rules for determining whether a medication is prior, concomitant, or post-treatment, are specified in Section 6.5.

5.4. Subject Disposition

The disposition of patients in the study will be summarized by treatment group and overall for FAS. Percentages will be calculated using the number of randomized patients as the denominator. The following summaries will be provided:

- The total number of screened patients who met the inclusion criteria regarding the target indication and signed the Informed consent form (ICF)
- The total number of randomized patients who 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

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The following listings will also be provided:

- 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

5.5. Extent of Study Treatment Exposure and Compliance

Exposure to study drug and compliance 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.

5.6. Analyses of Efficacy Variables

5.6.1. Analysis of Primary Efficacy Variable(s)

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 retinal fluid in the center subfield at week 16. The statistical analysis will be performed using chi-square test at the 2-sided 5% significance level. The 95% CIs will be provided based on normal approximation. P-value will also be provided for comparing the proportion of patients without retinal fluid at week 16 in HD versus IAI.

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.

- LOCF analysis:

  Missing observations are imputed by the last non-missing post-baseline observation. Patients will be considered as non-responders if all post-baseline observations are missing. For any patient who receives additional treatment at week 16, i.e., rescue, upon discussion with the Sponsor, their measurements at time points past week 16 will be imputed using the last observation prior to additional treatment at week 16. For remaining patients, their observed data at time points past week 16 will be included as usual.

LOCF procedure has been used in previous ophthalmology studies. Therefore, LOCF method will be used in this HD phase 2 study.

The following sensitivity analyses are used for the primary efficacy variable:

- Observed case (OC) analysis

  Measurements taken after the initiation of additional treatment at week 16 will be censored; only observed and non-censored values will be used for analysis, (i.e. missing data will not be imputed).

In the following analyses, the value at the given timepoint will be used regardless of whether the patient received additional treatment or not. Two different analyses will be conducted:

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- Ancillary LOCF (aLOCF) – Data obtained after the initiation of additional treatment will be included; missing data will be imputed by LOCF. Patients will be considered as non-responders if all post-baseline observations are missing. The data will be analyzed in the same way as described for the primary analysis.
- Ancillary observed case (aOC) - All observed values will be used for analysis, including measurements taken after the initiation of additional treatment is given. Missing data will not be imputed. The data will be analyzed in the same way as described for the primary analysis.

Note: up to and including week 16, aLOCF and LOCF analyses are identical, and so are aOC and OC.

5.6.2. Analysis of Exploratory Efficacy Variables

For the following binary 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 IRF at week 16 and week 44
- The proportion of patients without SRF at week 16 and week 44
- The proportion of patients without Sub-RPE fluid at week 16 and week 44
- The proportion of patients able to maintain (defined as meeting the criteria for "dry" at least two consecutive visits and for all subsequent visits) dry retina (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 a covariate. Missing data will be imputed using LOCF procedure. The following sensitivity analyses will be done for efficacy endpoints: OC, aLOCF, and aOC as defined in Section 5.6.1. In addition, supportive analyses will be conducted for change in BCVA from baseline using mixed-model repeated measures (MMRM) analysis model (of which missing values will not be imputed explicitly). The model will include treatment group, visit as fixed factors as well as terms for the interaction between baseline and the visit and for the interaction between treatment and visit and baseline BCVA measurements as covariate.

5.6.3. Subgroup Analyses

There will be no pre-defined subgroup analyses in this study.

5.6.4. Control of Multiplicity

There will be no control for multiplicity.

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5.7. Analysis of Safety Data

The safety variables as defined in Section 4.6 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).

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs, 12-lead ECG and physical exams).

Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Appendix 11.3.

The summary of safety results will be presented for each treatment group.

5.7.1. Adverse Events

All AEs reported in this study will be coded using the currently available version of the MedDRA®. Coding will be to lowest level terms. The verbatim text, the PT, and SOC will be listed.

Period of observation: The observation period will be divided into three segments:

- 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 Treatment-emergent adverse events [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

TEAEs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period. 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, presented by SOC and PT (regardless of relationship to treatment)
- Treatment-related TEAEs presented by SOC and PT

TEAEs leading to permanent treatment discontinuation will be listed and summarized by treatment group.

TEAEs in the study eye related to the injection procedure and those related to the study drug, injection procedure and study conduct will be summarized separately.

Deaths will be listed and summarized by treatment group.

SAEs, drug-related TEAEs, drug-related SAEs, and TEAEs leading to discontinuation will be summarized in the same way as described for TEAE.

TEAEs will further be summarized by the following categories:

- Ocular TEAEs in the study eye

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- Ocular TEAEs in the fellow eye
- Non-ocular TEAEs

Counts will be provided according to treatment group for each PT within each SOC. Percentages will be calculated using the number of patients from the SAF in each treatment group.

Primary SOCs will be sorted according to decreasing frequency. Within each primary SOC, PTs will be sorted by decreasing frequency. For tables presenting severity of events, the worst severity will be chosen for patients with multiple instances of the same event.

APTC events, intraocular inflammation, hypertension and nasal mucosa events will be tabulated and listed. The detailed definitions of these special AEs are presented in Appendix 11.2. Please refer to APTC charter for more information for APTC events.

5.7.2. Surgeries

Treatment emergent surgeries will be summarized by the following categories:

- Ocular treatment emergent surgeries in the study eye
- Ocular treatment emergent surgeries in the fellow eye
- Non-ocular treatment emergent surgeries

5.7.3. Clinical Laboratory Measurements

Baseline clinical laboratory analytes and change from Baseline in clinical laboratory analytes to each scheduled assessment time will be summarized with descriptive statistics. Summary statistics will include the number of patients, mean, median, standard deviation, quartiles, minimum, and maximum. The graphs of mean (or median) value of some lab parameters vs. visit will also be plotted.

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.

A treatment-emergent PCSV is a laboratory value that was normal at Baseline but met PCSV criteria after treatment with study drug. Definition of PCSV is listed in Appendix 11.3. Treatment Emergent PCSVs will be summarized based on the SAF and in the subgroup of SAF patients who do not meet the PCSV criterion at baseline.

5.7.4. Analysis of Vital Signs

Repeated post-dose blood pressure measurement are taken at week 4, week 8, week 9 (approximately 1 week after the third initial monthly dose), and then every 4 weeks from week 12 to week 44 for SAF. For the patients in the PK substudy, additional BP measures are taken at post dose days 2, 3, 5, 8, 15 and 22.

Vital signs (heart rate, systolic/diastolic BP, and temperature) will be summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics. The Baseline for BP is defined as the average of all 3 valid measurements taken prior to administration of study drug. The Baseline for other vital signs endpoints will be the latest

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available valid measurement taken prior to the administration of study drug, as specified in Section 6.1. The graphs of mean (or median) value of some vital sign parameters vs. visit will also be plotted. For additional BP analysis, please see the paragraphs below.

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Blood Pressure (main study)

In addition to the descriptive analysis above, changes in systolic BP and diastolic BP will be assessed using a time-weighted average for all timepoints up to week 9. All available BP measurements up to week 9 will be included for patients in the SAF (whether in PK substudy or not). The time-weighted average change from baseline in systolic BP and diastolic BP will be calculated as the Area Under the Curve (AUC) divided by the total duration in days. For patients who do not have available measurement at last visit, AUC will be calculated up to the last available measurements. AUC = 0 for patients who have no post-baseline measurements or changes from baseline were all 0 at all visits.

One-sided 95% confidence intervals will be created using normal approximation for changes in systolic BP and diastolic BP based on time-weighted average change from baseline, separately for each treatment group (IAI and HD). A nominal p-value for a one sample t-test for an alternative hypothesis of mean time-weighted average change from baseline <= 3 mm Hg will be presented for exploratory purpose.

Blood Pressure (PK substudy)

For the patients in the PK substudy, changes in systolic and diastolic BP will be assessed as described above (change from baseline to each scheduled assessment and time-weighted average from baseline to week 9). Like the main study, one-sided 95% confidence intervals and a nominal p-value will be presented.

In addition, adverse events of hypertension will be tabulated and listed (see Appendix 11.2) and changes in anti-hypertensive medications including changes in dose for these medications over the course of the study will be evaluated.

5.7.5. Analysis of 12-Lead ECG

ECG parameters (PR interval, QT interval, QRS interval, Ventricular rate and Heart rate) will be summarized by Baseline and change from Baseline to each scheduled and collected assessment time. PCSV summary of ECG parameters will be provided for the SAF.

ECG status (i.e. normal, abnormal) will be reported. Shift tables will be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) by treatment group.

5.7.6. Analysis of Ocular Safety Variables

Baseline IOP and change from Baseline in IOP to each scheduled assessment visit will be summarized with descriptive statistics for study eye and fellow eye. Assessment of significant values or increases will be made and summarized for the proportion of patients with increased IOP in the study eye or fellow eye with the categories defined in Section 4.6.6.

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5.8. Analysis of Pharmacokinetic Data

5.8.1. Analysis of Drug Concentration Data

Main Study:

The concentrations of free, bound, adjusted bound, and total 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, adjusted bound, and total 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.

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.

5.8.2. Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

Exposure-response analyses for systemic and ocular response variables may be performed, as appropriate.

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6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of study drug.

6.2. Visit Windows

The visits used for the analysis will be based on the nominal visits, i.e., according to the case report form (CRF) assessment recorded by the investigator. No visit windows will be further defined.

6.3. Unscheduled Assessments

Unscheduled assessments will not be included in the summaries.

If more than one value is available for a given visit, the visit value actually used for statistical summaries and analyses will be as follows:

- The last non-missing repeated measurement, if respective visit is before start of treatment
- The first non-missing repeated measurement, if respective visit is after start of treatment

If an early termination visit is performed within the window (±1 week) of the next scheduled visit after the last previous visit, the efficacy assessment will be re-slotted to the next scheduled visit.

6.4. Handling of Patients who Discontinue

Patients who discontinue this study will not be replaced. The details for the handling of missing data due to patients who discontinue the study and study medication are described in Section 6.5.

6.5. Data Handling Convention for Missing Data

For the primary and exploratory efficacy variables, missing observations will be imputed using LOCF. The details are described in the efficacy analysis section (Section 5.6).

Pretreatment/concomitant medication

For the tabulation of pretreatment and concomitant medication, partially missing start dates of the medication will be imputed by the earliest possible time point, partially missing stop dates will be imputed by the latest possible time point.

Adverse event

For some AEs it is important to determine whether the AE started before or after the first active aflibercept injection. If the AE start date is partially missing, it will be imputed by the latest possible date (considering other available data, e.g., stop date) to be conservative.

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7. INTERIM ANALYSIS

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

Analysis of data will be conducted for the prespecified primary analyses at the following timepoints:

- When all patients have reached week 4 (primary safety endpoint)
- When all patients have reached week 16 (primary efficacy endpoint)

In addition, a review of the safety and efficacy data will occur periodically throughout the conduct of the study.

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8. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher.

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9. SUMMARY OF MEASURES AND ANALYSES ADDRESSING IMPACT OF COVID-19

In light of the public health emergency related to COVID-19, in accordance with the regulatory guidance (2020) and in order to ensure the clinical study patient's safety and the continuity of clinical study conduct and oversight, the following measures are explored and implemented for this study conduct and analysis:

1. A Regeneron-standard CRF is implemented to collect COVID-19 related information:
   - **Subject's Visit Impact due to COVID-19:**
     - Entire visit not performed
     - Partial face to face visit
     - Remote Visit (Phone, Tele-medicine/Skype etc.)
     - Hybrid Visit (Partial face to face AND Remote Visit)
     - Home Visit by site staff or home health services
   - **Reasons**:
     - Subject unable to travel due to COVID-19
     - Subject/Guardian under quarantine due to COVID-19
     - Limited site personnel availability due to COVID-19
     - Site closure due to COVID-19
     - Other
   - **Discontinuation of treatment due to COVID-19**
   - **Reasons:**
     - Subject has COVID-19
     - Subject decided to stop due to COVID-19
     - Subject can no longer travel due to COVID-19
     - Physician decision due to COVID-19
     - Sponsor decision due to COVID-19
     - Other
   - **Discontinuation of study due to COVID-19**
   - **Reasons**:
     - Subject has COVID-19
     - Subject decided to stop due to COVID-19
     - Subject can no longer travel due to COVID-19

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- Physician decision due to COVID-19
- Sponsor decision due to COVID-19
- Other

- **Complete the AE form if subject tested positive or has symptoms of COVID-19**

Missed visits and discontinuation treatment/study due to COVID-19 will be summarized by treatment group and overall for FAS.

2. An updated version of MedDRA version 23.0 is to be released on 19 April 2020 to include new COVID-19 terms. The study team is to implement this re-released version 9823.0 by 4 May 2020, in line with the currently established procedure
3. Since some sites may suspend onsite study visits or patients may opt not to attend, to address the impact of missing data due to COVID-19 on efficacy analysis, additional subgroup analyses (such as including only patients who have received all 3 loading doses) may be performed as sensitivity analysis to evaluate the robustness of the efficacy results.

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 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

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10. REFERENCES

ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, Guidance for Industry, Investigators, and Institutional Review Boards, March 2020

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11. APPENDIX

11.1. Schedule of Time and Events

11.1.1. Schedule of Events for the Study

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

Table 2: 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 informed consent[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
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

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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
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
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

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 sub-study 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 sub-study ICF. This ICF will also include language for patients to consent to participate in the optional FBR study.

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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 2.1.
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 electronic data capture (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 3.
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 3.

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18. Week 4 collection of urinalysis/UPCR only for patients in the dense PK substudy.
19. Dense PK sampling will be performed in 30 patients (15 in each group) drawn according to the schedule in Table 3. On dosing days, PK samples must be collected prior to study drug administration.
20. Sparse PK sampling will be performed in all patients not enrolled in the dense PK substudy according to the schedule defined in Table 2. On dosing days, PK samples should be collected prior to study drug administration.
21. Exploratory research serum sample should be drawn prior to the administration of study drug at screening and week 44.

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11.1.2. 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 3.

Table 3: 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	
			4 (post-dose)	X		
			8 (post-dose)	X		
		2	±2h[3]	X	X	
		3	±2h[3]	X	X	
		5	±2h[3]	X	X	
		8	±2h[3]	X	X	X
		15	±2h[3]	X	X	X
		22	±2h[3]	X	X	

1. Timing of all BP assessment must be within 2 hours of the time of dosing on day 1.
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. PK draw for all assessment days are to be performed within ±2 hours of to the time of dosing on day 1.

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11.2. Detailed Definition of special AEs

11.2.1. Hypertension

Preferred term
Accelerated hypertension
Blood pressure ambulatory increased
Blood pressure diastolic increased
Blood pressure inadequately controlled
Blood pressure increased
Blood pressure systolic increased
Diastolic hypertension
Endocrine hypertension
Essential hypertension
Hypertension
Hypertension neonatal
Hypertensive angiopathy
Hypertensive cardiomegaly
Hypertensive cardiomyopathy
Hypertensive cerebrovascular disease
Hypertensive crisis
Hypertensive emergency
Hypertensive encephalopathy
Hypertensive end-organ damage
Hypertensive heart disease
Hypertensive nephropathy
Hypertensive urgency
Labile hypertension
Malignant hypertension
Malignant hypertensive heart disease
Malignant renal hypertension
Maternal hypertension affecting foetus
Mean arterial pressure increased
Neurogenic hypertension
Orthostatic hypertension
Prehypertension
Renal hypertension
Renovascular hypertension
Retinopathy hypertensive
Supine hypertension

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Preferred term
Systolic hypertension
White coat hypertension

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11.2.2. Intraocular inflammation

Preferred term
Anterior chamber cell
Anterior chamber flare
Anterior chamber inflammation
Anterior chamber fibrin
Aqueous fibrin
Autoimmune uveitis
Candida endophthalmitis
Chorioretinitis
Choroiditis
Cyclitis
Endophthalmitis
Eye infection intraocular
Eye inflammation
Hypopyon
Infective iritis
Infective uveitis
Infectious iridocyclitis
Iridocyclitis
Iritis
Mycotic endophthalmitis
Non-infectious endophthalmitis
Non-infective chorioretinitis
Pseudoendophthalmitis
Serpiginous choroiditis
Uveitis
Vitreal cells
Vitreous fibrin
Vitritis

11.2.3. Nasal mucosal events

Epistaxis
Nasal mucosa atrophy
Nasal mucosa blistering
Nasal mucosa discolouration
Nasal mucosa disorder
Nasal mucosa erosion
Nasal mucosa hypertrophy
Nasal mucosa ulcer
Nasal turbinate abnormality
Nasal turbinate hypertrophy

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Nasal septum haematoma
Nasal septum perforation
Nasal septum ulceration
Nasal cavity toxicity
Nasal necrosis
Nasal ulcer
Cautery to nose

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11.3. Criteria for Potentially Clinically Significant Values (PCSV)

Table 4: Criteria for Potentially Clinically Significant Values

Parameter	Potentially clinically significant value (PCSV)
Clinical Chemistry	
ALT	By distribution analysis : > 3 ULN
AST	By distribution analysis : > 3 ULN
Alkaline Phosphatase	> 1.5 ULN
Total Bilirubin	> 1.5 ULN
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN
CPK	> 3 ULN
Creatinine	≥ 150 µmol/L (Adults) ≥ 30% from baseline
Uric Acid	Hyperuricemia: >408 µmol/L Hypouricemia: <120 µmol/L
Blood Urea Nitrogen	≥ 17 mmol/L
Chloride	< 80 mmol/L > 115 mmol/L
Sodium	≤ 129 mmol/L ≥ 160 mmol/L
Potassium	< 3 mmol/L ≥ 5.5 mmol/L
Total Cholesterol	≥ 7.74 mmol/L (3 g/L)
Triglycerides	≥ 4.6 mmol/L (4 g/L)
Lipasemia	≥ 3 ULN
Glucose - Hypoglycaemia - Hyperglycaemia	 ≤ 3.9 mmol/L and < LLN ≥ 11.1 mmol/L (unfasted), ≥ 7 mmol/L (fasted)
HbA1c	> 8 %
Albumin	≤ 25 g/L
Hematology	
WBC	< 3.0 GIGA/L (non-Black), < 2.0 GIGA/L (Black), ≥ 16.0 GIGA/L
Lymphocytes	> 4.0 GIGA/L
Neutrophils	< 1.5 GIGA/L (non-Black) < 1.0 GIGA/L (Black)
Monocytes	> 0.7 GIGA/L
Basophils	> 0.1 GIGA/L
Eosinophils	> 0.5 GIGA/L or > ULN if ULN ≥ 0.5 GIGA /L

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Parameter	**Potentially clinically significant value (PCSV)**
Hemoglobin	Males : ≤115 g/L (≤ 7.14 mmol/L), ≥ 185 g/L (11.48 mmol/L) Females : ≤ 95 g/L (5.9 mmol/L), ≥ 165 g/L (10.24 mmol/L) Decrease from Baseline ≥ 20 g/L (1.24 mmol/L)
Hematocrit	Males : ≤ 0.37 v/v, ≥ 0.55 v/v Females : ≤ 0.32 v/v, ≥ 0.5 v/v
RBC	≥ 6 TERA/L
Platelets	< 100 GIGA/L ≥ 700 GIGA/L

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11.4. Process to Derive Week 16 Data Cut-off

For week 16 evaluations, a strategy for performing the data cut-off for the clinical database was developed, as described in the following:

11.4.1. Visit Dependent Data

All visit dependent data up to week 16 (visit 8 will be kept for the week 16 analysis. All visit dependent data later than week 16 (visit 8) will not be included for the week 16 analysis. Unscheduled visits with a date prior to the week 16 (visit 8) visit date will be kept for the week 16 analysis. If a patient did not have a week 16 (visit 8) visit, unscheduled visit will be kept up to date of first injection + 112 days for the week 16 analysis.

11.4.2. Visit Independent Data

Visit independent data (or event based data) include adverse events, concomitant/prior medication, and surgical/medical history.

Patients that discontinued study prematurely before or at week 16 (Visit 8)

These patients are defined as having their end of study CRF page filled, and have either:

- a dropout date earlier or equal to date of first injection + 112 days or
- a dropout date earlier or equal to week 16 visit date

For such patients, all event based records are kept in the clinical database for week 16 analysis without any change.

Patients who stayed longer than week 16 (Visit 8) in the study

These patients are the patients who did not discontinue study prematurely at/before week 16 (visit 8). Therefore, these patients are either:

- still ongoing after week 16 (visit 8),
- discontinued the study prematurely, but were in the study for longer than week 16 (visit 8).

For such patients, the following will be applied:

All event records with a start date later than the date of the week 16 (visit 8) will be censored. This includes the case where the incomplete date is without any doubt later than the week 16 visit date, e.g. week 16 (visit 8) is 10 April 2020 and the incomplete date is May 2020 or only 2021. If the week 16 visit date is missing, then the date of first injection + 112 days will be used instead.

Records with a start date earlier or equal to the date of week 16 (first injection + 112 days if date of week 16 is missing) will be kept (this includes incomplete dates when the incomplete date is earlier than the week 16 date or in cases where it is not clear if the record occurred before or after week 16, e.g., week 16 (visit 8) is 10 April 2020 and the incomplete date is March 2020, April 2020 or only 2020 or even a missing date, but several adaptions to the data will be made):

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Concomitant medication:

If a stop date is reported which is earlier than the date of week 16 (visit 8) (first injection + 112 days if date of week 16 is missing), the record will not be changed.

If a stop date is reported which is later than the date of week 16 (visit 8) (first injection + 112 days if date of week 16 is missing), the stop date will be set to missing and the variable CMONG will be set to 1 (yes).

Adverse Events:

AEs with a start date on or after the date of the week 16 (visit 8) will be censored. Cut-off date will be first injection + 112 days if date of week 16 is missing.

If a stop date of adverse event is specified and earlier or equal to date of week 16 (visit 8) (first injection + 112 days if date of week 16 missing), then the record will not be changed.

If a stop date of adverse event is specified and later than the date of week 16 (visit 8) (first injection + 112 days if date of week 16 is missing), then the stop date will be set to missing and the outcome of the adverse event (SAS variable AEOUT) will be set to missing.

If no stop date is specified and the outcome is either not yet reported (AEOUT is blank) or is reported (AEOUT is 3 - recovering/resolving, 4 - not recovered/not resolved, 6 - unknown), then the outcome will be set to missing (AEOUT is blank).

Surgeries:

All surgeries with a date of surgery later than week 16 (visit 8) date will be deleted.

11.4.3. Study Medication Data

Study medication data up to week 12 (visit 7) will be kept for the week 16 analysis.

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11.5. Process to Derive Week 4 Data Cut-off

For week 4 evaluations, same strategy for performing the data cut-off for the clinical database as described in Appendix 11.4 will be followed. Instead of "first injection + 112 days" for week 16, missing dates for week 4 will be imputed by first injection + 28 days.

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