Clinical Study Protocol

A STUDY IN PATIENTS WITH DIABETIC MACULAR EDEMA OR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TO EVALUATE A HIGH DOSE AFLIBERCEPT (8 MG) PREFILLED SYRINGE

Compound:	Aflibercept 8 mg
Clinical Phase:	3b
Protocol Number:	VGFTe-HD-OD-22105
Protocol Version:	VGFTe-HD-OD-22105 Amendment 1
Amendment 1 Date of Issue:	*See appended electronic signature page*
Original Date of Issue	14 June 2023
Medical /Study Director:	[redacted]

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

AMENDMENT HISTORY

Amendment 1

The primary purpose for this amendment is update the introduction with EYLEA HD® approval language and to update inclusion criteria to match the study design.

Description of Change	Brief Rationale	Section # and Name
Addition of language for EYLEA HD® approval in the introduction.	To update the introduction to include the approval language for EYLEA HD®	Section 1 Introduction
Inclusion criteria #4: language was removed, ie, "signed by study patient or legally acceptable representative", and inclusion criteria #5 was removed.	For inclusion #4, this study will not enroll participants who lack capacity and, therefore, require a legally authorized representative (LAR), and inclusion #5 has been removed due to no study-related questionnaires conducted during this study.	Section 7.2.1 Inclusion Criteria

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
BCVA	Best Corrected Visual Acuity
BP	Blood pressure
BRVO	Branch retinal vein occlusion
COVID-19	Coronavirus Disease 2019
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRVO	Central retinal vein occlusion
CTFG	Clinical Trial Facilitation Group
DME	Diabetic macular edema
DR	Diabetic retinopathy
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GPS	Global Patient Safety
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IOP	Intraocular pressure
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IVT	Intravitreal
mCNV	Myopic choroidal neovascularization
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	Neovascular age-related macular degeneration
PFS	Pre-filled syringe
PT	Preferred term
RBQM	Risk-Based Quality Monitoring
Regeneron	Regeneron Pharmaceuticals, Inc.

RVO	Retinal vein occlusion
SAE	Serious adverse event
SAF	Safety analysis set
SAS	Statistical analysis software
SD-OCT	Spectral domain optical coherence tomography
SDR	Source data review
SDV	Source data verification
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
US	United States
VA	Visual acuity
WOCBP	Women of childbearing potential

TABLE OF CONTENTS

AMENDMENT HISTORY 2
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 3
CLINICAL STUDY PROTOCOL SYNOPSIS 9
1. INTRODUCTION 12
2. STUDY OBJECTIVES 13
2.1. Primary Objective 13
2.2. Secondary Objective 13
3. HYPOTHESIS AND RATIONALE 14
3.1. Hypotheses 14
3.2. Rationale 14
3.2.1. Rationale for Study Design 14
3.2.2. Rationale for Dose Selection 14
3.3. Risk-Benefit 14
4. ENDPOINTS 15
4.1. Primary and Secondary Endpoints 15
4.1.1. Primary Endpoint 15
4.1.2. Secondary Endpoint 15
5. STUDY VARIABLES 16
5.1. Demographic and Baseline Characteristics 16
5.2. Investigator Determination of Successful 8 mg Aflibercept PFS Injection 16
5.3. Safety Variables 16
6. STUDY DESIGN 17
6.1. Study Description and Duration 17
6.1.1. End of Study Definition 17
6.2. Planned Interim Analysis 17
7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS 18
7.1. Number of Patients Planned 18
7.2. Study Population 18
7.2.1. Inclusion Criteria 18
7.2.2. Exclusion Criteria 18
7.3. Premature Withdrawal from the Study 20

7.4. Replacement of Patients 20
8. STUDY TREATMENTS....21
8.1. Investigational and Reference Treatments....21
8.2. Dose Modification and Study Treatment Discontinuation Rules 21
8.2.1. Dose Modification 21
8.2.2. Study Drug Discontinuation 21
8.3. Method of Treatment Assignment 21
8.4. Masking 21
8.5. Treatment Logistics and Accountability....21
8.5.1. Packaging, Labeling, and Storage 21
8.5.2. Supply and Disposition of Treatments 22
8.5.3. Treatment Accountability 22
8.5.4. Treatment Compliance....22
8.6. Concomitant Medications and Procedures 22
8.6.1. Prohibited Medications....22
8.6.2. Permitted Medications and Procedures 23
9. STUDY SCHEDULE OF EVENTS AND PROCEDURES 24
9.1. Schedule of Events 24
9.1.1. Footnotes for the Schedule of Events Table 26
9.1.1.1. Table 1 Schedule of Events 26
9.1.2. Early Termination Visit 26
9.1.3. Unscheduled Visits 26
9.2. Study Procedures 26
9.2.1. Procedures Performed Only at the Screening/Baseline Visit 26
9.2.2. Ocular Safety Study Procedures 27
9.2.2.1. Best Corrected Visual Acuity 27
9.2.2.2. Intraocular Pressure 27
9.2.2.3. Slit Lamp Examination 27
9.2.2.4. Indirect Ophthalmoscopy....27
9.2.2.5. Spectral Domain Optical Coherence Tomography....27
9.2.3. Non-Ocular Safety Procedures 27
9.2.3.1. Vital Signs 27
9.2.3.2. Urine Pregnancy Test 27

10. SAFETY EVALUATION AND REPORTING 28
10.1. Recording and Reporting Adverse Events 28
10.1.1. General Guidelines 28
10.1.2. Reporting Procedure 29
10.1.3. Events that Require Expedited Reporting to Sponsor 29
10.2. Definitions 29
10.2.1. Adverse Event 29
10.2.1.1. Serious Adverse Event 30
10.2.1.2. Severity 31
10.2.1.3. Causality 31
10.2.2. Device Incidents 32
10.3. Safety Monitoring 32
10.4. Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators 33
11. STATISTICAL PLAN 34
11.1. Statistical Hypothesis 34
11.2. Justification of Sample Size 34
11.3. Analysis Sets 34
11.3.1. Safety Analysis Set 34
11.4. Statistical Methods 34
11.4.1. Patient Disposition 34
11.4.2. Demography and Baseline Characteristics 34
11.4.3. Primary Analysis 34
11.4.4. Safety Analysis 35
11.4.4.1. Adverse Events 35
11.4.4.2. Ocular Safety 35
11.4.4.3. Other Safety 35
11.4.4.4. Treatment Exposure 35
11.4.4.5. Treatment Compliance 35
11.5. Additional Statistical Data Handling Conventions 36
11.6. Statistical Considerations Surrounding the Premature Termination of a Study 36
12. QUALITY CONTROL AND QUALITY ASSURANCE 37
12.1. Data Management and Electronic Systems 37

12.1.1. Data Management 37
12.1.2. Electronic Systems 37
12.2. Study Monitoring 37
12.2.1. Monitoring of Study Sites 37
12.2.2. Source Document Requirements 38
12.2.3. Case Report Form Requirements 38
12.3. Audits and Inspections 38
12.4. Study Documentation 39
12.4.1. Certification of Accuracy of Data 39
12.4.2. Retention of Records 39
13. ETHICAL AND REGULATORY CONSIDERATIONS 40
13.1. Good Clinical Practice Statement 40
13.2. Informed Consent 40
13.3. Patient Confidentiality and Data Protection 40
13.4. Institutional Review Board 41
13.5. Clinical Study Data Transparency 41
14. PROTOCOL AMENDMENTS 42
15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE 43
15.1. Premature Termination of the Study 43
15.2. Close-out of a Site 43
16. CONFIDENTIALITY 44
17. FINANCING AND INSURANCE 45
18. PUBLICATION POLICY 46
19. INVESTIGATOR'S AGREEMENT 47
SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS 48

LIST OF TABLES

Table 1: Schedule of Events 25

LIST OF FIGURES

Figure 1: Study Flow Diagram 17

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Study in Patients with Diabetic Macular Edema or Neovascular Age-Related Macular Degeneration to Evaluate a High Dose Aflibercept (8 mg) Prefilled Syringe
Site Locations	Approximately 2 sites in the United States (US)
Objectives	The primary objective of the study is to determine if the PFS can be used successfully by retina specialists to administer the 8 mg dose of aflibercept. The secondary objective is to assess ocular safety in the study eye.
Study Design	This is a phase 3b, single-arm, open-label study in patients with diabetic macular edema (DME) and/or neovascular "wet" age-related macular degeneration (nAMD) to evaluate use of the aflibercept 8 mg PFS. The study will consist of a screening period, a single aflibercept injection on day 1, and a follow-up period through day 29. After providing informed consent, patients will be assessed for study eligibility at the screening visit, held up to 2 weeks before the day 1 (baseline) visit. Screening and the day 1 (baseline) visit may occur on the same day. Only 1 eye can be selected as the study eye. At the day 1 (baseline) visit, patients will undergo safety assessments followed by a single injection of the study drug, administered with the PFS by a retina specialist. There will be a follow-up period of 28 days with a window of –7 days to +14 days, during which patients will be monitored and evaluated for safety. Ocular adverse events (AEs) in the study eye and all ocular and non-ocular serious adverse events (SAEs) will be captured.
Study Duration	The duration of the study for a patient is approximately 29 days, excluding the screening period.
End of Study Definition	The end of the study is defined as the last visit of the last patient.
Population	
Sample Size:	Approximately 35 patients will be enrolled at 2 sites in the US.
Target Population:	The study population will include men or women with treatment-naïve or previously-treated DME or nAMD, in whom treatment with aflibercept 8 mg is warranted based on the investigator's evaluation.

Treatments	
Study Drug **Dose/Route/Schedule:**	The drug product will be supplied as a sterile aqueous solution for injection in a PFS. The aflibercept 8 mg PFS is a single-dose 0.5 mL glass syringe with a luer connection for a needle and is provided in sealed blister pack. Each single-dose PFS provides a usable amount to deliver a single dose of aflibercept 8 mg via intravitreal (IVT) injection. The PFS, enclosed in a sealed blister pack utilized in this study, is filled with an aflibercept concentration of 114.3 mg/mL. The PFS is representative of the presentation intended for commercialization in the US. Only 1 eye will be selected as the study eye by the investigator. Patients will receive a single dose of aflibercept 8 mg, prepared and administered with the PFS, at the day 1 (baseline) visit.
Endpoints	
Primary:	Investigator determination of successful 8 mg aflibercept PFS injection at day 1. Successful injection for a given patient is defined as administration of the prescribed dose consistent with the instructions for use as assessed by the injecting physician.
Secondary:	Incidence of ocular AEs in the study eye (including SAEs) through day 29.
Procedures and Assessments	Ocular safety procedures will include Best Corrected Visual Acuity (BCVA), assessed using the 4-meter Early Treatment Diabetic Retinopathy Study (ETDRS); intraocular pressure (IOP); slit lamp examination; indirect ophthalmoscopy; and spectral domain optical coherence tomography (SD-OCT). Overall safety will be assessed by evaluation of ocular AEs in the study eye, and all (ocular and non-ocular) SAEs.
Statistical Plan	The sample size of approximately 35 patients for this study is based on US Food and Drug Administration (FDA) advice and is not determined from power analysis. The safety analysis set (SAF) will include all enrolled patients who received any study drug, and it will be used for all study analyses. The primary endpoint will be analyzed as the proportion of investigator-determined successful injections in the SAF. Both frequency and percentages will be displayed. Descriptive statistics will be provided for the other endpoints. For continuous variables, the descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, standard

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

1. INTRODUCTION

The efficacy and safety of intravitreal (IVT) aflibercept has been well characterized across multiple indications in numerous clinical trials. Marketing authorizations have been granted for aflibercept 2 mg (EYLEA®, [aflibercept] injection) in over 108 countries for the treatment of patients with neovascular "wet" age-related macular degeneration (nAMD), including the United States (US), countries in the European Union (EU), Japan, and Australia. IVT aflibercept injection is also approved for the treatment of patients with macular edema following central retinal vein occlusion (CRVO) in over 104 countries, macular edema following branch retinal vein occlusion (BRVO) in over 98 countries, diabetic macular edema (DME) in over 103 countries, and myopic choroidal neovascularization (mCNV) in over 95 countries. In addition to nAMD, DME, and retinal vein occlusion (RVO), aflibercept is also approved in the US for the treatment of diabetic retinopathy (DR) in patients with DME. Currently, aflibercept 2 mg is available as a sterile aqueous solution for injection in both single use, glass vials and a 1 mL pre-filled syringe (PFS) with a dosing line.

Increasing the drug product 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. Regeneron Pharmaceuticals, Inc. (hereafter, Regeneron [sponsor]) has developed a novel formulation of 8 mg aflibercept that has been studied in the pivotal studies PHOTON in the DME population and PULSAR in the nAMD population. Aflibercept 8 mg (EYLEA HD®) is approved for use in the US for the treatment of nAMD, DME and DR since 18 Aug 2023. Currently, aflibercept 8 mg is available as a sterile aqueous solution for injection in a single use, glass vial. Regeneron has developed a single-dose 0.5 mL glass PFS to deliver aflibercept 8 mg without the need for a dosing line. The PFS minimizes the number of manipulations required to prepare an injection delivered with a vial presentation. Each single-dose PFS provides a usable amount to deliver a single dose of aflibercept 8 mg in a volume of 70 µL. The PFS is provided in a sealed blister pack and is being proposed for commercial use.

This study is intended to investigate if the aflibercept 8 mg PFS allows for successful preparation and administration by retina specialists.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to determine if the PFS can be used successfully by retina specialists to administer the 8 mg dose of aflibercept.

2.2. Secondary Objective

The secondary objective of the study is to assess ocular safety in the study eye.

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

The Regeneron-designed aflibercept 8 mg PFS will be used by retina specialists to successfully deliver the 8 mg dose in patients with DME or nAMD.

There is no formal statistical hypothesis in this study.

3.2. Rationale

3.2.1. Rationale for Study Design

This study is intended to confirm that the single-dose 0.5 mL PFS provided in a sealed pack supports successful preparation and administration of an injection of aflibercept 8 mg in a 70 µL volume, performed by retina specialists. Per regulatory agency (US Food and Drug Administration [FDA]) feedback during a Type C Meeting (29 Nov 2021), a clinical study of approximately 30 patients utilizing the proposed commercial aflibercept PFS configuration would likely be sufficient for approval and is proposed here.

3.2.2. Rationale for Dose Selection

The dose used in this study is aflibercept 8 mg delivered in a volume of 70 µL. This dose is supported by results from the phase 2 CANDELA (nAMD), the phase 2/3 PHOTON (DME), and phase 3 PULSAR (nAMD) studies.

3.3. Risk-Benefit

The clinical development program of aflibercept 8 mg provides robust evidence of its clinical benefit and safety. The safety profile of aflibercept 8 mg has been investigated in a clinical trial program, including 2 large pivotal studies in the indications of nAMD and DME (PULSAR and PHOTON) and 1 supportive study in nAMD (CANDELA). Overall, 1217 patients were treated with aflibercept 8 mg in these studies.

The safety profile of IVT aflibercept 8 mg is consistent with the well-established safety profile of aflibercept 2 mg based on extensive clinical development and real-world experience available for aflibercept 2 mg. It includes identified risks such as intraocular inflammation/infection, retinal tear, retinal detachment, transient increase in intraocular pressure (IOP), traumatic cataract, and hypersensitivity. Other safety topics that are known to be associated with the systemic administration of anti-VEGF medications for cancer treatment include arteriothromboembolic events, embryo-fetotoxicity, and an increase in blood pressure (BP). The secondary objective of this study is to assess patient ocular safety in the study eye. Safety will be assessed by evaluation of ocular adverse events (AEs) in the study eye, and all (ocular and non-ocular) serious adverse events (SAEs).

Overall Risk-Benefit Balance:

A risk-benefit statement with respect to the overall development program is provided in Section 7 of the Investigator's Brochure (IB). Based on the available data, the benefit-risk assessment of aflibercept 8 mg is considered positive and supports the clinical trial program.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

The primary endpoint in the study is the investigator determination of successful 8 mg aflibercept PFS injection at day 1.

Successful injection in a given patient is defined as administration of the prescribed dose consistent with the instructions for use as assessed by the injecting physician.

4.1.2. Secondary Endpoint

The secondary endpoint is the incidence of ocular AEs in the study eye (including SAEs) through day 29.

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc); disease characteristics, including medical and ocular history; and medication history for each patient.

5.2. Investigator Determination of Successful 8 mg Aflibercept PFS Injection

The investigator's determination of a successful 8 mg aflibercept PFS injection will be recorded as a "yes" or "no" in the source documents and electronic data capture (EDC) system.

5.3. Safety Variables

Safety will be evaluated by assessing ocular AEs in the study eye, ocular and non-ocular SAEs, ocular examination including Best Corrected Visual Acuity (BCVA), IOP, and vital signs (temperature, sitting BP, and pulse).

6. STUDY DESIGN

6.1. Study Description and Duration

This is a phase 3b, single-arm, open-label study in patients with DME or nAMD to evaluate the use of the aflibercept 8 mg PFS. The study will consist of a screening period, a single aflibercept injection on day 1, and a follow-up period through day 29.

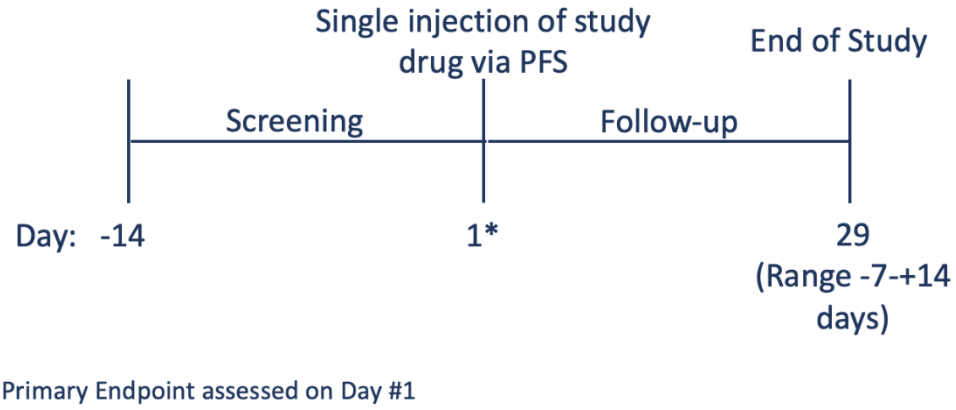
After providing informed consent, patients will be assessed for study eligibility at the screening visit, to be scheduled up to 2 weeks before the day 1 (baseline) visit. Screening and the day 1 (baseline) visit may also occur on the same day. Only 1 eye will be selected as the study eye by the investigator.

At the day 1 (baseline) visit, patients will undergo safety assessments followed by a single injection of the study drug, prepared by a retina specialist and/or technician, and administered with the PFS by a retina specialist.

There will be a follow-up period of 28 days with a window of –7 days to +14 days, during which patients will be monitored and evaluated for safety. Ocular AEs in the study eye and all ocular and non-ocular SAEs will be captured.

The study flow diagram is shown in Figure 1.

Figure 1: Study Flow Diagram



PFS = pre-filled syringe

6.1.1. End of Study Definition

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

6.2. Planned Interim Analysis

No interim analysis is planned.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 35 patients will be enrolled at 2 sites in the US.

7.2. Study Population

The study population will include men or women with treatment-naïve or previously-treated DME or nAMD, in whom treatment with aflibercept 8 mg is warranted based on the investigator's evaluation.

7.2.1. Inclusion Criteria

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

1. Men or women ≥18 years of age who have DME or nAMD in the study eye
2. Study eye considered by the retina specialist to be eligible for treatment with aflibercept 8 mg
3. Willing and able to comply with clinic visits and study-related procedures
4. Provide informed consent

7.2.2. Exclusion Criteria

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

1. Evidence of ocular or periocular infection including active infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye
2. History of hypersensitivity to aflibercept or any excipients in aflibercept 8 mg
3. Any active intraocular inflammation or infection in either eye or history of intraocular inflammation or infection after past IVT injections with any agent in either eye
4. History of or any current indication of excessive bleeding and recurrent hemorrhages, including any prior excessive intraocular (including subconjunctival) bleeding or hemorrhages after IVT injection or intraocular procedures in either eye
5. Treatment with any IVT injection in the study eye within the 25 days prior to day 1
6. IOP >25 mm Hg in the study eye at screening
7. Count fingers or worse vision in one or both eyes
8. Use of therapies that are known to be toxic to any ocular tissues (eg, radiation) in either eye
9. Any intraocular surgery in the study eye at any time during the past 3 months
10. Any prior extended-release therapeutic agent, or ocular drug-release device implantation (approved or investigational, including steroids) in the study eye
11. 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 safety

12. Participation as a patient in any interventional clinical study within the 12 weeks prior to day 1 of the study
13. Concurrent enrollment in any investigational study, including the extension phase of PHOTON or PULSAR
14. Current systemic infectious disease or a therapy for active infectious disease
15. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor
16. Pregnant or breastfeeding women
17. Men or women of childbearing potential (WOCBP)* 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 4 months (120 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 occlusion/ligation;
    d. vasectomy**;
    e. condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly, and/or
    f. sexual abstinence[†, ‡].

    *WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

    **Vasectomized study patients or vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study patients). Vasectomized partner or vasectomized study patients must have received medical assessment of the surgical success for the procedure.

†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 drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

‡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.

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 9.1.2.

7.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

The drug product will be supplied as a sterile aqueous solution for injection in a PFS. The 8 mg PFS is a single-dose 0.5 mL glass syringe with a luer connection for a needle and is provided in a sealed blister pack.

Each single-dose PFS delivers a single 8 mg dose of aflibercept (114.3 mg/mL) via IVT injection. The PFS, enclosed in a sealed blister pack utilized in this study, is representative of the presentation intended for commercialization in the US. [redacted] A ½ inch 30-gauge needle is recommended.

Instructions on dose preparation and administration will be provided to investigators and are included in the pharmacy manual.

Any issues with the device that prevent successful injection should be reported to the sponsor immediately via guidelines presented in the study manual and documented as appropriate. Such devices should not be used and be retained. The investigator will be advised to contact the sponsor as soon as possible and refer to the study manual for instructions regarding reporting and return.

8.2. Dose Modification and Study Treatment Discontinuation Rules

8.2.1. Dose Modification

Dose modification for an individual patient is not allowed.

8.2.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments per Section 9.1.2.

8.3. Method of Treatment Assignment

Not applicable, as this is an open-label study without a control group.

8.4. Masking

Not applicable, as this is an open-label study without a control group.

8.5. Treatment Logistics and Accountability

8.5.1. Packaging, Labeling, and Storage

Open-label study drug will display the product lot number on the label.

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

8.5.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee as needed during the study. During the study at the site close-out visit and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be returned to the sponsor or designee.

8.5.3. Treatment Accountability

All drug accountability records must be kept current.

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

- dispensed to each patient
- disposed of in the designated sharps container that will be 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.

8.5.4. Treatment Compliance

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

8.6. Concomitant Medications and Procedures

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

COVID-19 vaccination, either as an initial series or as a booster dose, received during the study, will be treated as a concomitant medication. As noted, administration of a COVID-19 vaccination should be separated from the time of administration of the investigational product (at least 72 hours, ideally by at least one week) in order to avoid confounding the effects (eg, adverse effects) of the vaccine/booster with the effects of study drug.

Patients enrolled in a trial involving the administration of investigational product who wish to receive a COVID-19 vaccine should postpone the administration of the vaccine until 21 days following the last dose of study drug.

8.6.1. Prohibited Medications

Patients may not receive any medications (approved or investigational) for their DME or nAMD in the study eye other than the assigned study treatment (aflibercept) as specified in this protocol unless they have completed the end-of-study (day 29) visit assessments. This includes medications administered locally (eg, IVT, topical, juxtascleral, or periorbital routes), as well as those administered systemically, with the intent of treating the study eye.

8.6.2. Permitted Medications and Procedures

Standard-of-care treatment will be allowed for any ocular condition in the fellow eye at any time during the study. At the physician's discretion, the patient's fellow eye may receive treatment on the same day as the study eye or at an unscheduled visit. All fellow eye treatments must be recorded on the CRF as a concomitant medication and/or procedure for the fellow eye. The fellow eye will not be considered an additional study eye. Patients who receive treatment for the fellow eye will not be required to be withdrawn from the study.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1.

Table 1: Schedule of Events

	Screening Visit[1]	Combined Screening/Baseline Visit[1]	Baseline Visit[1]	End-of-Study Visit
Study Procedure	**Visit 1**	**Visit 1 and 2**	**Visit 2**	**Visit 3**
Day	–14 to 1	1	1	29 (–7 to +14)
Screening/Baseline:				
Inclusion/Exclusion	X	X[2]		
Informed Consent (ICF)	X	X[2]		
Medical History	X	X[2]		
Demographics	X	X[2]		
Pregnancy Test Urine (WOCBP)[8]	X	X[2]		
Treatment:				
Review of Concomitant Meds	X	X[2]	X[2]	X
Administer Intravitreal Aflibercept via PFS		X[3]	X[3]	
Safety:				
BCVA (ETDRS) and refraction[4]	X	X[2]	X[2]	X
IOP[5]	X	X	X	X
Slit lamp examination[4]	X	X[2]	X[2]	X
Indirect ophthalmoscopy[6]	X	X	X	X
SD-OCT[7]	X	X[2]	X[2]	X
Vital signs (Temperature, BP, HR)	X	X[2]	X[2]	X
Adverse events (ocular study eye and all serious adverse events)	X	X	X	X

BCVA = Best Corrected Visual Acuity, BP = Blood pressure, ETDRS = Early Treatment Diabetic Retinopathy Scale, HR = Heart rate, ICF = Informed consent form, IOP = Intraocular pressure, PFS = Pre-filled syringe, SD-OCT = Spectral domain optical coherence tomography, WOCBP = women of childbearing potential.

9.1.1. Footnotes for the Schedule of Events Table

9.1.1.1. Table 1 Schedule of Events

1. The screening and baseline visits may be conducted separately (visit 1 and visit 2) or may be combined (visit 1 and 2); however, assessments and procedures do not need to be duplicated.
2. Must be completed before administration of aflibercept 8 mg
3. A single IVT injection of aflibercept 8 mg will be administered on day 1 or as part of the combined screening/baseline visit. The pharmacy manual will contain instructions for use. Patients will be observed for approximately 30 minutes following study drug injection.
4. BCVA and slit lamp examination will be performed bilaterally at all study visits.
5. IOP will be measured bilaterally at all study visits. On the day when the study drug is administered, IOP should be measured pre-dose (bilaterally) and approximately 30 minutes after administration of the study drug in the study eye only.
6. Indirect ophthalmoscopy will be performed bilaterally at all study visits. On the day when the study drug is administered, indirect ophthalmoscopy should be performed pre-dose and immediately after administration of the study drug (study eye only).
7. The same SD-OCT imaging system used at the screening and baseline visit(s) must be used at all visits in each patient (study eye only).
8. For WOCBP, a negative urine pregnancy test at screening and baseline is required for enrollment.

9.1.2. Early Termination Visit

Patients who are withdrawn from the study before the end-of-study visit (day 29) will be asked to return to the clinic once for an early termination visit consisting of the end-of-study assessments described in Table 1.

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary 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 and demographics.

9.2.2. Ocular Safety Study Procedures

9.2.2.1. Best Corrected Visual Acuity

Visual function will be assessed using the 4-meter Early Treatment Diabetic Retinopathy Study (ETDRS) scale at time points according to Table 1. Visual acuity examiners must be certified to ensure consistent measurement of BCVA. Current certification from any study requiring the 4M ETDRS will be accepted. The patient's BCVA, based on their most recent/current refraction, if they wear glasses or contact lenses, will be accepted. A separate manifest refraction will not be required.

9.2.2.2. Intraocular Pressure

IOP will be measured using Goldmann applanation tonometry or Tono-pen™, at time points according to Table 1. The same method of IOP measurement must be used throughout the study for each individual patient.

9.2.2.3. Slit Lamp Examination

Patients' anterior eye structure and ocular adnexa will be examined by the investigator using a slit lamp at time points according to Table 1.

9.2.2.4. Indirect Ophthalmoscopy

Patients' posterior pole and peripheral retina will be examined by the investigator using indirect ophthalmoscopy at time points according to Table 1.

9.2.2.5. Spectral Domain Optical Coherence Tomography

Retinal characteristics in the study eye will be evaluated by the investigator using SD-OCT at time points according to Table 1.

9.2.3. Non-Ocular Safety Procedures

9.2.3.1. Vital Signs

Vital signs, including temperature, sitting BP, and pulse, will be collected predose at time points according to Table 1 and at the end-of-study visit.

9.2.3.2. Urine Pregnancy Test

For WOCBP, a negative urine pregnancy test at screening and baseline is required for enrollment.

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, from the time of signing the Informed Consent Form (ICF) to the end of the day 29 visit (see Section 11.4.4.1). Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal 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. AEs 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 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.

Vital signs and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance. Vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, 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 SAE (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 ICF 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 AEs, 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 and concomitant medications 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**.
- **Selected Adverse Events of Special Interest** (AESI; serious and nonserious)**:** No AESIs have been defined for this study.
- **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 4 months (120 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).

10.2.1.1. 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).

Criteria for Serious Sight-Threatening Ocular Adverse Events

Criteria for serious sight-threatening ocular AEs include the following:

- AE causes a decrease in BCVA of >30 letters (compared with the most recent assessment of BCVA)
- AE causes a decrease in visual acuity (VA) to the level of light perception or worse
- AE requires surgical intervention (eg, vitreous tap or biopsy with IVT injection of anti-infectives, laser or retinal cryopexy with gas) to prevent permanent loss of sight
- AE is associated with severe intraocular inflammation (ie, 4 + anterior chamber cell/flare or 4 + vitritis)
- In the opinion of the investigator, AE may require medical intervention to prevent permanent loss of sight

Criteria for reporting SAEs must be followed for these events.

10.2.1.2. 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.

10.2.1.3. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the AE, 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 (including study drug administration):

- 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 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.

10.2.2. Device Incidents

All PFS devices will be collected and returned to the sponsor. Detailed instructions for the collection and return of these PFS devices will be provided to the investigator in the study manual. Product Technical Complaint (PTC) is defined as any reported complaint regarding the use of the PFS. All PFS associated with a PTC will be investigated by the sponsor and the sponsor will assign causality according to the findings of the investigation.

The sponsor plans to assess device incidents using the following classifications:

- **Device Malfunction** - the failure of a device constituent part or of the product as a whole to meet its performance specifications or otherwise perform as intended.
- **Device Misuse** - any intentional act or intentional omission of an act that is counter to or violates normal use and is also beyond any further reasonable means of user interface-related risk control by the sponsor.
- **Medication Error** - any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional.

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, Global Patient Safety [GPS]; 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 /Ethics Committee, and Investigators

During the study, the sponsor and/or the contract research organization (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.

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

There will be no formal statistical analyses for this study. Only descriptive statistics will be employed.

11.1. Statistical Hypothesis

There is no statistical hypothesis in this study.

11.2. Justification of Sample Size

The sample size of approximately 35 patients for this study is based on FDA advice and is not determined from power analysis.

11.3. Analysis Sets

11.3.1. Safety Analysis Set

The safety analysis set (SAF) will include all enrolled patients who received any study drug. Treatment administration and all clinical safety variables will be analyzed using the SAF.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, standard deviation, 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 enrolled patients
- The total number of patients who discontinued the study, and the reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

11.4.3. Primary Analysis

For the primary endpoint, the proportion of injections deemed successful will be tabulated; the frequency/percentage will be displayed.

11.4.4. Safety Analysis

11.4.4.1. Adverse Events

Definitions

The on-treatment period is defined as the time from the day when the single dose of the study drug is administered through the day 29 visit.

Treatment-emergent AEs (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.

Analysis

Summaries of all TEAEs will include the number (n) and percentage (%) of patients with:

- TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.1.2), presented by SOC and PT
- Treatment-related TEAEs, presented by SOC and PT
- AEs leading to deaths
- SAEs
- TEAEs leading to study discontinuation

11.4.4.2. Ocular Safety

In addition to ocular AEs and SAEs in the study eye, IOP measurements will be analyzed descriptively at the scheduled visits, including changes from baseline. All ocular safety, including BCVA parameters will be summarized using descriptive statistics. Information from SD-OCT may also be used to assess ocular safety.

11.4.4.3. Other Safety

Vital Signs

Vital signs (including temperature, sitting BP, and pulse) will be summarized.

11.4.4.4. Treatment Exposure

The extent of exposure to the investigational drug (characterized according to the number of patients exposed) will be detailed in the tables and listings.

11.4.4.5. Treatment Compliance

Not applicable, as each patient only receives a single study drug injection.

11.5. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The baseline assessment is defined as the latest valid predose assessment

General rules for handling missing data:

If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.

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.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, medications, medical history/surgical history/ophthalmic history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

The CRF data for this study will be collected with an EDC tool, 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:

- EDC system – data capture- Medidata RAVE
- Statistical analysis software (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk-based quality principles, outlined in International Council for Harmonisation (ICH) E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

The study monitor and/or designee (eg, CRO monitor) will visit each site prior to enrollment of the first patient.

The investigator must allow study-related monitoring.

The study monitors will perform ongoing SDR 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, and 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 eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRF 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. Patient Confidentiality and Data Protection

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

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

13.4. Institutional Review Board

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

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. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: "A Study in Patients with Diabetic Macular Edema or Neovascular Age-Related Macular Degeneration to Evaluate a High Dose Aflibercept (8 mg) Prefilled Syringe" 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 report accurately describes the planned conduct of the study.

Study Title: A Study in Patients with Diabetic Macular Edema or Neovascular Age-Related Macular Degeneration to Evaluate a High Dose Aflibercept (8 mg) Pre-filled Syringe

Protocol Number: VGFTe-HD-OD-22105

Protocol Version: VGFTe-HD-OD-22105 Amendment 1

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-00325660 v1.0

Approval/eSignature	[redacted] 22-Nov-2023 12:14:34 GMT+0000

Approval/eSignature	[redacted] 22-Nov-2023 13:25:43 GMT+0000

Approval/eSignature	[redacted] 22-Nov-2023 15:15:06 GMT+0000

Approval/eSignature	[redacted] 22-Nov-2023 19:58:49 GMT+0000

Signature Page for VV-RIM-00325660 v1.0 Approved