Clinical Study Protocol

A STUDY IN PATIENTS WITH CHORIORETINAL VASCULAR DISEASE TO EVALUATE AN AFLIBERCEPT (EYLEA®) PREFILLED SYRINGE

Compound:	Aflibercept (EYLEA®)
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AMENDMENT HISTORY

Amendment 4

To describe the continuity plan for conducting clinical study activities and study oversight activities during the public health emergency due to COVID-19.

Description of Change	Brief Rationale	Section # and Name
Added language related to the COVID-19 pandemic.	To describe the continuity plan for conducting clinical study activities and study oversight activities during the public health emergency due to COVID-19.	Section 8.1 Schedule of Events Section 3.3 Risk-Benefit (new section)
Revised the description of the diabetic retinopathy indication	To reflect current approval status.	Section 1 Introduction

Amendment 3

The purpose of this amendment is to enroll an additional 35 patients to be treated with the aflibercept prefilled syringe (PFS), per health authority request. The aflibercept PFS to be supplied for these additional patients will also represent a presentation intended for commercialization with some components originating from a different supplier than the PFS used for the initial 35 patients. The initial 35 patients will now be referred to as cohort 1, and the additional 35 patients will be called cohort 2.

Change	Sections Changed
Added an additional 35 patients to be enrolled and treated with the aflibercept PFS.	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Population/ Sample Size Clinical Study Protocol Synopsis: Statistical Plan Section 3.1 Rationale for Study Design Section 5.1 Study Description and Duration Section 6.1 Number of Patients Planned Section 10 Statistical Plan Section 10.2 Justification of Sample Size

Amendment 2

The purpose of this amendment is to add a statement that the prefilled syringe (PFS) utilized in this study reflects the presentation intended for commercialization, per health authority request.

Change	Sections Changed
Added a statement that the PFS utilized in this study reflects the presentation intended for commercialization	Clinical Study Protocol Synopsis: Treatments Section 7.1 Investigational and Reference Treatments
Minor editorial correction to Amendment History for amendment 1	Amendment History

Amendment 1

The purpose of this administrative amendment is to revise the wording to provide a more general description of the prefilled syringe ("externally sterilized" and "tamper-evident tip cap" were removed), which will allow for introduction of clinical supply without contradiction in the protocol description. Study design rationale was also clarified, because the study isn't measuring accuracy of the drug administration.

Change	Sections Changed
Removed "externally sterilized" and "tamper-evident tip cap" (and associated wording as necessary)	Clinical Study Protocol Synopsis (Treatments: Study Drug Dose/Route/Schedule) Section 1 Introduction Section 7.1 Investigational and Reference Treatments
Clarified study design rationale	Section 3.1 Rationale for Study Design

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Study in Patients with Chorioretinal Vascular Disease to Evaluate an Aflibercept (EYLEA®) Prefilled Syringe
Site Locations	Approximately 2 sites in the United States (US)
Objectives	The primary objective of the study is to determine if the prefilled syringe (PFS) can be used effectively and safely by retina specialists to administer the 2 mg dose of aflibercept. The secondary objective of the study is to assess ocular safety in the study eye.
Study Design	This is a phase 4, single-arm (2-cohort), open-label study in patients with chorioretinal vascular disease (neovascular age-related macular degeneration [AMD], diabetic macular edema [DME], retinal vein occlusion [RVO], and diabetic retinopathy [DR] in patients with DME) to evaluate handling of the aflibercept PFS. The study consists of a screening period, a single aflibercept treatment, and a follow-up period. The initial 35 patients will now be referred to as cohort 1, and the additional 35 patients will be called cohort 2. After providing informed consent, patients will be assessed for study eligibility at the screening visit, up to 2 weeks before the day 1/baseline visit. Screening and the day 1/baseline visit can occur on the same day. Only 1 eye will be selected as the study eye. At the day 1/baseline visit, patients will undergo safety assessments, and will then receive a single dose of study drug, prepared (retina specialist and/or technician) and administered with the PFS by a retina specialist. There is a follow-up period of 28 days with a window of -7 days to +14 days, during which patients will be evaluated for safety (ocular adverse events [AEs] and all [ocular and non-ocular] serious adverse events [SAEs]).
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 study is defined as the last visit of the last patient.
Population	
Sample Size:	Approximately 70 patients will be enrolled, 35 patients in each of 2 cohorts, at approximately 2 sites in the US.
Target Population:	The study population will include men or women with treatment-naïve or previously-treated neovascular AMD, DME, RVO, or DR with DME, in whom treatment with aflibercept is indicated.

Treatment(s)	
Study Drug **Dose/Route/Schedule:**	The drug product is supplied as a sterile aqueous solution for injection in a PFS. The PFSs are single-use 1 mL glass syringes with a luer connection for the needle, and are provided in sealed blister packs. Each single-dose PFS provides a usable amount to deliver a single dose of 2 mg aflibercept in a volume of 50 µL, via intravitreal (IVT) injection. The PFS utilized in this study is fully representative of the presentation intended for commercialization. Only 1 eye will be selected as the study eye Patients receive a single dose of aflibercept, prepared and administered with the PFS, at the day 1/baseline visit.
Endpoints	
Primary:	The primary endpoint in the study is the number of aflibercept injections successfully administered utilizing the PFS.
Secondary:	The secondary endpoint is the ocular safety of aflibercept delivered in the PFS. Safety will be measured by the incidence of ocular AEs and SAEs in the study eye.
Procedures and Assessments	Ocular safety procedures will include Best Corrected Visual Acuity (BCVA) scale, 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 per cohort 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) includes all enrolled patients who received any study drug, and it will be used for all study analyses. 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
AMD	Neovascular age-related macular degeneration
BCVA	Best Corrected Visual Acuity
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
DME	Diabetic macular edema
DR	Diabetic retinopathy
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Scale
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IOP	Intraocular pressure
IRB	Institutional Review Board
IVT	Intravitreal
mCNV	Myopic choroidal neovascularization
MedDRA	Medical Dictionary for Regulatory Activities
PFS	Prefilled syringe
PT	Preferred term
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
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
US	United States

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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 (EYLEA®, [aflibercept] injection), in over 108 countries for the treatment of patients with neovascular "wet" age-related macular degeneration (AMD) including the United States (US), countries in the European Union (EU), Japan, and Australia. Intravitreal 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 neovascular AMD, DME, and retinal vein occlusion (RVO), aflibercept is also approved in the US for the treatment of diabetic retinopathy (DR).

Currently, aflibercept is available as a sterile aqueous solution for injection in single-use, glass vials. Each vial provides a usable amount to deliver a single dose of 2 mg aflibercept in a volume of 50 µL. This configuration requires withdrawal of aflibercept using a 19-gauge × 1½-inch, 5 µM, filter needle into a 1 mL syringe. Prior to injection the filter needle is replaced with 30-gauge × ½-inch injection needle. These steps are performed using aseptic technique.

To minimize the number of manipulations required to prepare the injection, Regeneron has developed a single-use 1 mL glass prefilled syringe (PFS). Each single-dose, PFS provides a usable amount to deliver a single dose of 2 mg aflibercept in a volume of 50 µL.

This study is intended to investigate if the 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 effectively and safely by retina specialists to administer the 2 mg dose of aflibercept.

2.2. Secondary Objective

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

3. RATIONALE

3.1. Rationale for Study Design

This study is intended to confirm that the single-dose PFS supports successful preparation and administration of an aflibercept injection by retina specialists. Per regulatory agency feedback, a clinical study of at least 30 patients in each of 2 cohorts utilizing each of the proposed commercial aflibercept PFS configurations will be conducted.

3.2. Rationale for Dose Selection

The dose proposed for this study is the 2 mg dose of aflibercept approved by the Food and Drug Administration (FDA) for the treatment of neovascular AMD, RVO, DME, and DR in patients with DME.

3.3. Risk-Benefit

3.3.1. COVID-19 Pandemic

Recognizing that "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any patient in this study in a specific location or area until the COVID-19 pandemic is controlled and such that patients can safely participate in the study. Until then, the Sponsor plans to continue to obtain approvals from Health Authorities/Ethics Committees (ECs) to enable initiation of study sites for this study, as allowed by local laws and regulations.

4. STUDY VARIABLES

4.1. 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.

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The primary endpoint in the study is the number of aflibercept injections successfully administered utilizing the PFS.

4.2.2. Secondary Endpoint

The secondary endpoint in the study is the ocular safety of aflibercept delivered in the PFS. Safety will be measured by the incidence of ocular adverse events (AEs) and serious adverse events (SAEs) in the study eye, through day 29.

5. STUDY DESIGN

5.1. Study Description and Duration

This is a phase 4, single2-arm (2-cohort), open-label study in patients with chorioretinal vascular disease (neovascular AMD, DME, RVO, and DR in patients with DME) to evaluate use of the aflibercept PFS. The study consists of a screening period, a single aflibercept treatment, and a follow-up period through day 29. The initial 35 patients will now be referred to as cohort 1, and the additional 35 patients will be called cohort 2.

After providing informed consent, patients will be assessed for study eligibility at the screening visit, up to 2 weeks before the day 1/baseline visit. Screening and the day 1/baseline visit can occur on the same day. Only 1 eye will be selected as the study eye.

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

There is a follow-up period of 28 days with a window of -7 days to +14 days, during which patients will be evaluated for safety (ocular AEs and all [ocular and non-ocular] SAEs.

5.1.1. End of Study Definition

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

5.2. Planned Interim Analysis

No interim analysis is planned.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Approximately 70 patients will be enrolled, 35 patients in each of 2 cohorts, at approximately 2 sites in the US.

6.2. Study Population

The study population will include men or women with treatment-naïve or previously-treated neovascular AMD, DME, RVO, or DR with DME, in whom treatment with aflibercept is indicated.

6.2.1. 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 neovascular AMD, DME, RVO, or DR with DME in the study eye
2. Study eye considered by the retina specialist to be indicated for treatment with aflibercept
3. Willing and able to comply with clinic visits and study-related procedures
4. Provide informed consent signed by study patient or legally acceptable representative
5. Able to understand and complete study-related questionnaires

6.2.2. Exclusion Criteria

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

1. Evidence of active infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye
2. 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
3. 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
4. Treatment with any IVT injection in the study eye within the 28 days prior to day 1
5. Intraocular pressure (IOP) >25 mm Hg in the study eye at screening
6. Count fingers or worse vision in one or both eyes
7. Use of therapies that are known to be toxic to any ocular tissues (eg, radiation) in either eye
8. Any intraocular surgery in the study eye at any time during the past 3 months
9. Any prior extended-release therapeutic agent, or ocular drug-release device implantation (approved or investigational including steroids) in the study eye
10. 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
11. Participation as a patient in any interventional clinical study within the 12 weeks prior to day 1 of the study
12. Current systemic infectious disease or a therapy for active infectious disease
13. Pregnant or breastfeeding women
14. Women of childbearing potential*

    *Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential.

6.3. 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 study assessments, as described in Section 8.1.2.

6.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

The drug product is supplied as a sterile aqueous solution for injection in a PFS. The PFS(s) are single-use 1 mL glass syringes with a luer connection for the needle, and are provided in sealed blister packs.

Each single-dose PFS provides a usable amount to deliver a single dose of 2 mg aflibercept in a volume of 50 µL, via IVT injection. The PFS(s) utilized in this study are fully representative of the presentations intended for commercialization as submitted in the aflibercept IND, Module P.2.4 Container Closure System, SN 0810. Only 1 eye will be selected as the study eye.

Instructions on dose preparation are provided in the pharmacy manual.

7.2. Dose Modification and Study Treatment Discontinuation Rules

7.2.1. Dose Modification

Dose modification for an individual patient is not allowed.

7.3. Method of Treatment Assignment

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

7.3.1. Masking

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

7.4. Treatment Logistics and Accountability

7.4.1. 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 will be provided in the pharmacy manual.

7.4.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed / returned to the sponsor or designee.

7.4.3. Treatment Accountability

All drug accountability records must be kept current.

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

- dispensed to each patient,
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.4.4. Treatment Compliance

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

7.5. 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.

7.5.1. Prohibited Medications and Procedures

Patients may not receive any medications (approved or investigational) for their AMD, DME, RVO, or DME with DR 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.

7.5.2. Permitted Medications and Procedures

Standard-of-care treatment will be allowed for any ocular condition in the fellow eye at any time during the trial. 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 case report form (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.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

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

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

Table 1: Schedule of Events

Study Procedure	Screening[1] Visit 1	Combined Screening/Baseline Visit[1] Visit 1/2	Baseline[1] Visit 2	End of Study Visit 3
Day	-14 to -1	1	1	29 (-7 to +14 days)
Screening/Baseline:				
Inclusion/exclusion	X	X[2]		
Informed consent	X	X[2]		
Medical history	X	X[2]		
Demographics	X	X[2]		
Treatment:				
Review of concomitant meds	X	X[2]	X[2]	X
Administer intravitreal aflibercept		X[3]	X[3]	
Safety:				
Slit lamp examination	X	X[2]	X[2]	X
Indirect ophthalmoscopy	X	X[4]	X[4]	X
SD-OCT	X	X[2]	X[2]	X
ETDRS 4M BCVA	X	X[2]	X[2]	X
Intraocular Pressure	X	X[5]	X[5]	X
Adverse events (ocular study eye and all serious adverse events)	X	X	X	X

SD-OCT=spectral domain optical coherence tomography, ETDRS= Early Treatment Diabetic Retinopathy Scale, BCVA= Best Corrected Visual Acuity

8.1.1. Footnotes for the Schedule of Events Table

1. The screening and baseline visits may be conducted separately (visit 1 and visit 2) or may be combined (visit 1/2), but assessments and procedures will not be duplicated.
2. Must be completed prior to administration of aflibercept.
3. A single intravitreal injection of aflibercept will be given once on day 1 or as part of the combined screening/day 1 visit.
4. Indirect ophthalmoscopy will be performed pre-dose and immediately after administration of study drug (study eye only).
5. Intraocular pressure will be measured pre-dose and approximately 30 minutes after administration of study drug (study eye only).

8.1.2. 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 for an early termination visit consisting of the end-of-study assessments described in Table 1.

8.1.3. 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.

8.2. Study Procedures

8.2.1. 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.

8.2.2. Ocular Safety Procedures

8.2.2.1. Best Corrected Visual Acuity

Visual function of the study eye 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 Best Corrected Visual Acuity (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 is not required.

8.2.2.2. Intraocular Pressure

Intraocular pressure of the study eye 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. Intraocular pressure will be measured pre-dose (study eye) by the investigator (or designee), and at approximately 30 minutes post-dose (study eye) by the investigator (or designee).

8.2.2.3. Slit Lamp Examination

Patients' anterior eye structure and ocular adnexa (study eye) will be examined pre-dose by the investigator using a slit lamp (study procedure manual), at time points according to Table 1.

8.2.2.4. Indirect Ophthalmoscopy

Patients' posterior pole and peripheral retina in the study eye will be examined pre-dose and immediately after administration of study drug (study eye only) by the investigator by indirect ophthalmoscopy, at time points according to Table 1.

8.2.2.5. Spectral Domain Optical Coherence Tomography

Retinal characteristics will be evaluated by the investigator using spectral domain optical coherence tomography (SD-OCT), at time points according to Table 1.

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB) all unanticipated problems involving risks to patients, according to local regulations. This may include death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB, according to local regulations.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, IRBs as appropriate, and to the investigators.

Any AE not listed as an expected event in the Reference Safety Information section of the Investigator's Brochure will be considered as unexpected. Any worsening of or new onset of symptoms related to (add underlying condition intended to be studied) which occur during the screening/washout period prior to study drug administration will be considered expected.

In addition, the sponsor will report in all other SAEs to the health authorities, according to local regulations.

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.

9.3. Definitions

9.3.1. Adverse Event

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

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

9.3.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 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:

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

Criteria for reporting SAEs must be followed for these events. See Section 9.4 for more information on recording and reporting SAEs.

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all ocular study eye AEs and any SAEs (ocular and systemic) that occur from the time the informed consent is signed until the end of study. Refer to the study reference manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 9.4.5.

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manual for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study or early termination visit - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

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

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE,

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 90 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest (AESI): No AESIs have been defined for this study.

Refer to the study manual for the procedures to be followed.

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's Medical/Study Director within 30 days.

Refer to the study reference manual for the procedures to be followed.

9.4.5. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

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

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

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the study drug?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug is resumed
- are not a suspected response to the study drug based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug
- resolve or improve after discontinuation of study drug
- reappear or worsen when dosing with study drug
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

Relationship of AEs to Injection Procedure:

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

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

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the injection procedure

Related: There is a reasonable possibility that the event may have been caused by the injection procedure

The sponsor will request information to justify the causality assessment of SAEs, as needed.

A list of factors to consider in assessing the relationship of AEs to injection procedure, study procedure, or background treatment, etc. is provided below. Please note that this list is not exhaustive.

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

No:

- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the injection procedure
- do not reappear or worsen when the injection procedure is resumed
- are not a suspected response to the injection procedure based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the injection procedure
- resolve or improve after discontinuation of study drug or injection procedure
- reappear or worsen when the injection procedure is resumed
- are known or suspected to be a response to injection procedure based upon preclinical data or prior clinical data

9.6. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the reference safety information in the Investigator's Brochure, and has a reasonable suspected causal relationship to the study drug).

10. STATISTICAL PLAN

There will be no formal statistical analyses for this study. Only descriptive statistics will be employed. Cohort 1 and cohort 2 will be analyzed separately. There are no plans to either compare the individual results from the 2 cohorts, or to analyze the 2 cohorts in a combined manner.

10.1. Statistical Hypothesis

There is no statistical hypothesis in this study.

10.2. Justification of Sample Size

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

10.3. Analysis Sets

10.3.1. Safety Analysis Set

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

10.4. 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.

10.4.1. 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

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

10.4.3. Safety Analyses

10.4.3.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the informed consent form (ICF) to before the first dose of study drug.
- The treatment period is defined as the day when the single dose of study drug was administered.
- The posttreatment period is defined as the time after administration of the single dose of study drug through the day 29 visit.

Treatment-emergent adverse events (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

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized.

10.4.3.2. 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 parameters will be summarized using descriptive statistics. Information from OCT may also be used to assess ocular safety.

10.4.3.3. Treatment Exposure

- The number of aflibercept injections successfully administered utilizing the PFS will be summarized.
- The extent of exposure to the investigational drug (characterized according to the number of patients exposed) will be detailed in the tables and listings.

10.4.3.4. Treatment Compliance

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

10.5. 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 pre-dose 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.

10.6. 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 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. 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 done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) tool, Medidata RAVE.

11.2. 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
- Statistical analysis software (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12. STUDY MONITORING

12.1. Monitoring of Study Sites

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

The investigator must allow study-related monitoring.

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

12.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on paper CRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each 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.

13. AUDITS AND INSPECTIONS

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

Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection

Providing access to all necessary facilities, study data, and documents for the inspection or audit

Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately

Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

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

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

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. 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.

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, 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.

14.2. 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.

14.3. 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.

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB-approved amendment.

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

16.1. 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.

16.2. 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.

17. STUDY DOCUMENTATION

17.1. 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.

17.2. 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.

18. DATA 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 summarized.

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 11.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 12.1, Section 12.2, and Section 13).

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 12.1).

All patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient final CRF (Section 12.3 and Section 17.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 12.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 17.2).

19. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

20. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

21. PUBLICATION POLICY

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

22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Study in Patients with Chorioretinal Vascular Disease to Evaluate an Aflibercept (EYLEA®) Prefilled Syringe (PFS) 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 Team Lead, and Biostatistician)

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

Study Title: A Study in Patients with Chorioretinal Vascular Disease to Evaluate an Aflibercept (EYLEA®) Prefilled Syringe

Protocol Number: VGFTe-OD-1881

Protocol Version: VGFTe-OD-1881 Amendment 4

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 Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00107449 v1.0

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