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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 3B SINGLE-ARM STUDY OF AFLIBERCEPT 8 MG IN PARTICIPANTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (nAMD) OR DIABETIC MACULAR EDEMA (DME)

Compound:	Aflibercept
Study Name:	ELARA
Clinical Phase:	3b
Protocol Number:	VGFTe-HD-OD-2444
Protocol Version:	VGFTe-HD-OD-2444 Amendment 3
Amendment 3 Date of Issue:	*See appended electronic signature page*
Amendment 2 Date of Issue:	31 Oct 2024
Amendment 1 Date of Issue:	23 Sep 2024
Original Date of Issue	24 May 2024
Medical Director:	[redacted]

[redacted]

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AMENDMENT HISTORY

Rationale for Amendment 3

The main purpose of this amendment is to make clarifications in the operational aspects of this protocol primarily related to the visit windows and other procedures reflected in the SOE table.

The following table outlines the changes made to the protocol, with a brief rationale, and the affected sections:

Description of Change	Brief Rationale	Section # and Name
Corrected the study days and visit windows within the Schedule of Events (SOE) table.	Administrative update to correct errors in the SOE table.	Table 2 Schedule of Events
Visit window for the Mandatory visit was revised to ±17 days (previously ±16 days).	Administrative update to correct error.	Synopsis: Study Design Section 5.1 Study Description and Duration Section 8.1.1 Footnotes for the Schedule of Events Table, Footnote #3
Revised footnote #2 to indicate that, in addition to the Dosing visits already listed in the SOE, additional Dosing visits may occur at weeks 36, 48, 60, 72, and 84.	This update clarifies that Dosing visit can coincide with Mandatory visit and will be combined.	Section 8.1.1 Footnotes for the Schedule of Events Table, Footnote #2
Revision to allow sites to submit ultra-widefield color photographs instead of fundus photography (FP) for diabetic macular edema (DME) participants.	This change clarifies the flexibility in the required imaging equipment and assessments for each disease indication.	Section 8.2.1.5 Fluorescein Angiography/Fundus Photography
Dose regimen modification assessment added to week 96/End of Study visit.	This update allows for an accurate assessment of the last assigned interval for all participants.	Table 2 Schedule of Events
Sample size updated from “up to 1000” to “approximately 1000” participants.	To allow for an enrollment buffer at the site level based on logistical considerations for participant scheduling.	Synopsis: Study Design Synopsis: Population Synopsis: Statistical Plan Section 5.1 Study Description and Duration Figure 1 Study Flow Diagram Section 6.1 Number of Participants Planned Section 10.2 Justification of Sample Size

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Overall Rationale for Amendment 2

The main purpose of this amendment is to increase the sample size from approximately 400 participants to up to 1000 participants. In addition, details of the [redacted] have been included as an appendix to the protocol.

Description of Change	Brief Rationale	Section # and Name
Increase in sample size to up 1000 participants (~500 participants with nAMD and ~500 participants with DME)	An increase in the sample size from approximately 400 participants to up to 1000 participants will allow for a more robust understanding of Q4 week dosing with 8 mg aflibercept in participants with nAMD and DME from a safety perspective as well as a clinical standpoint. Uniquely, in this study, participants have been treated previously with other agents and may be treated bilaterally during the study, highlighting important treatment paradigms that are critical to understand. The expanded sample size will allow for more meaningful subgroup analyses in the future, based on many factors such as frequency and type of prior treatment, responsiveness to prior treatment, and baseline disease characteristics.	Synopsis Study Design and Treatment, Population, Statistical Analysis Plan Section 5.1 Study Description and Duration Figure 1 Study Flow Diagram Figure 2 Dosing Schedule Section 6.1 Number of Participants Planned Section 10.2 Justification of Sample Size
Revised text to clarify that fellow eye treatment will be allowed with aflibercept 8 mg at the investigator's discretion and supplied through IWRS	To provide flexibility in the drug supply for fellow eye treatment.	Section 7.1 Investigational and Reference Treatments
Added Appendix 1	[redacted].	Section 8.1.1 Footnotes for the Schedule of Events Table Section 8.2.1.1 Best-Corrected Visual Acuity Appendix 1 [redacted]
Minor edits	For clarity.	Throughout the protocol

Overall Rationale for Amendment 1

The purpose of this amendment is to provide clarity for the DRM criteria, the inclusion/exclusion criteria for the previously treated population being studied, and the requirement for prior/ongoing treatment for concomitant disease in the study and fellow eye.

Description of Change	**Brief Rationale**	**Section # and Name**
Updated the dose regimen modification (DRM) criteria and implementation	These changes were made to allow investigators to treat participants in a manner that reflects current practice patterns. With the updates, once shortened, the dosing interval will be maintained for 12 weeks and extension thereafter will be conservative (extension by 1 week intervals vs. 2) to optimally treat participants.	Synopsis Study Design and Treatment Section 5.1 Study Description and Duration Figure 2 Dosing Schedule Section 8.1 Schedule of Events Section 8.1.1 Footnotes for the Schedule of Events Table #2, #3, and #5
Updated inclusion/exclusion criteria	These updates provide guidance on the anatomic requirements for the participant population that is being studied, considering these participants have previously diagnosed and treated disease.	Section 6.2.3 Inclusion Criteria (Criteria #3 removed) Section 6.2.4 Exclusion Criteria (Criteria #11 removed)
Updated study-eye and fellow-eye eligibility criteria and concomitant medications	These updates allow for prior fellow eye treatment with approved anti-complement IVT treatment for GA and for this treatment to continue during the study.	Section 6.2.4 Exclusion Criteria Section 7.7.1 Prohibited Medications and Procedures
Removed the urine pregnancy collection from the EOS visit	Pregnancy test is performed at every visit where a dose is given in either the study eye or fellow eye. Pregnancy would lead to a participant being withdrawn. Since there is no study eye dosing at the EOS, there does not need to be a pregnancy test at this visit.	Section 8.1 Schedule of Events
Minor edits	For clarity.	Throughout the protocol

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

2q4	Aflibercept 2 mg every 4 weeks
2q8	Aflibercept 2 mg every 8 weeks
8q4	Aflibercept 8 mg every 4 weeks
AE	Adverse event
AESI	Adverse event of special interest
AOBP	Automated office blood pressure
ATE	Arteriothromboembolic event
BCVA	Best-corrected visual acuity
BP	Blood pressure
BRVO	Branch retinal vein occlusion
CNV	Choroidal neovascularization
COVID-19	Coronavirus disease 2019
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRVO	Central retinal vein occlusion
CSR	Clinical study report
CST	Central subfield thickness
CTFG	Clinical Trial Facilitation Group
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRCR	Diabetic Retinopathy Clinical Research
DRM	Dose regimen modification
DRM-E	Dose regimen modification criteria for extending
DRM-S	Dose regimen modification criteria for shortening
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End of study
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein angiography
FP	Fundus photography
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GPS	Global Patient Safety
HR	Heart rate

IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IOP	Intraocular pressure
IRB	Institutional Review Board
IRF	Intraretinal fluid
IUD	Intrauterine device
IUS	Intrauterine system
IVT	Intravitreal
IWRS	Interactive web response systems
LAM	Lactation amenorrhea method
mCNV	Myopic choroidal neovascularization
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
PK	Pharmacokinetic
PlGF	Placental growth factor
PRP	Panretinal photocoagulation
PT	Preferred term
q4	Every 4 weeks
Regeneron	Regeneron Pharmaceuticals, Inc.
RBQM	Risk-Based Quality Management
ROP	Retinopathy of prematurity
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD-OCT	Spectral domain optical coherence tomography
SDR	Source data review
SDV	Source data verification
SMT	Safety Monitoring Team
SOC	System organ class
SOE	Schedule of events
SRF	Subretinal fluid
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
VEGF	Vascular endothelial growth factor

US	United States
USPI	United States Prescribing Information
wAMD	Wet age-related macular degeneration
WOCBP	Women of childbearing potential
YAG	Yttrium-aluminum-garnet

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3b Single-Arm Study of Aflibercept 8 mg in Participants With Neovascular Age-Related Macular Degeneration (nAMD) or Diabetic Macular Edema (DME)
Short Title	A phase 3b, single-arm study of aflibercept 8 mg dosed every 4 weeks in participants with nAMD or DME.
Site Location(s)	Approximately 80 sites in the United States
Principal Investigator	TBD
Objectives and Endpoints	The primary objective of this study is to evaluate the safety of aflibercept 8 mg. Primary Endpoint: Occurrence of treatment-emergent adverse events (TEAEs) and serious TEAEs through week 24.
Study Design	This is a phase 3b, multicenter, single-arm study to assess the safety and measures of efficacy of treatment with aflibercept 8 mg dosed every 4 weeks (8q4) in participants with nAMD or DME previously treated with intravitreal (IVT) anti-vascular endothelial growth factor (VEGF) injections. This study consists of a screening/enrollment visit, a treatment period, and an end-of-study (EOS) visit at week 96. Eligibility will be assessed at the screening visit on day 1. Participants with nAMD or DME are eligible for screening if they have been previously treated with ≥3 anti-VEGF injections over the prior 5 months (~150 days). A total of approximately 1000 participants (~500 participants with nAMD and ~500 participants with DME) who meet all eligibility criteria will be enrolled. The screening visit should be held approximately 4 to 7 weeks (25 to 49 days) after the most recent anti-VEGF injection and, for eligible participants, the initial study treatment will occur on the same day. Participants will receive a total of 7 injections of aflibercept 8q4, from baseline through week 24. To assess the ability to extend dosing intervals with aflibercept 8 mg in this population, Dose Regimen Modification (DRM) criteria will be used to assess potential dose interval extensions, as well as subsequent dose interval shortening at each visit beginning at week 24. The minimum interval between injections is 4 weeks (28 days). **DRM-E:** Beginning at week 24, participants will be evaluated for dose interval extension. Dose intervals will be extended by 2 weeks when DRM-E criteria are met at any Dosing visit as long as the dose interval has not been shortened previously. For participants who have had their dose interval shortened

previously, the dose interval will only be extended by 1 week increments and only after a minimum of 12 weeks (84 days) has passed.

Participants will be eligible for interval extension if the following criteria are met at **any Dosing visit**:

nAMD

- No retinal fluid in central subfield

  AND
- No new onset foveal neovascularization or foveal hemorrhage

  AND
- No interval shortening within the last 12 weeks (84 days)

DME

- CST <300 µm [redacted]

  AND
- ≤10 µm increase (worsening) from lowest (best) previous CST value

  AND
- No interval shortening within the last 12 weeks (84 days)

DRM-S:

If a participant's interval has been extended, then the dose interval may be shortened by 1 week if the DRM-S criteria are met. If the DRM-S criteria are met at either a dosing or a non-dosing visit, the participant will be dosed, and the subsequent interval will be shortened to the time from the most recent dose minus 1 week. The minimum interval between injections will be every 4 weeks.

Participants will be eligible for interval shortening (by 1-week increments), if one of the following criteria are met at **any scheduled visit**:

nAMD

- Any new retinal fluid in the central subfield

  OR
- New onset foveal neovascularization or foveal hemorrhage

  OR
- >5 letter loss in BCVA from best previous attributable to recurrent or persistent disease

DME

- >25 µm increase in CST from previous visit

  OR
- >10 letter loss in BCVA from best previous attributable to recurrent or persistent disease

	DRM-E and DRM-S criteria will be assessed by the investigator. Participants who do not meet the above criteria for interval extension or shortening at a given visit will continue treatment at the current interval. Participants will be seen every 4 weeks through week 24. After week 24, participants will return for Dosing visits scheduled based on their DRM assessments. Dosing visits should be scheduled as close to the planned date as possible. Mandatory visits will occur approximately every 12 weeks through the EOS visit for all participants, regardless of dosing schedule. Mandatory visits can be moved to within the ±17-day visit window to be combined with Dosing visits when the visit windows overlap (except visit 13, week 96). Participants may be seen for unscheduled visits at the investigator's discretion at any time. The primary analysis will occur once all participants have completed week 24 (or prematurely discontinued), with the final analysis occurring after all participants have completed the study at week 96 (or prematurely discontinued). Additional analyses may be performed at other timepoints, eg, week 48. Safety will be assessed by ophthalmic exams, collection of vital signs (including heart rate [HR] and blood pressure [BP]), and by evaluating the occurrence of AEs and SAEs.
Study Duration	The duration of the study for a participant is approximately 96 weeks.
End of Study Definition	The definition for EOS is the last visit of the last participant in the study.
Population	
Sample Size:	The sample size for this study is approximately 1000 participants (~500 participants with nAMD and ~500 participant with DME).
Target Population:	Participants with nAMD or DME previously treated with at least 3 anti-VEGF injections in the 5 months (~150 days) prior to screening.
Treatment	
Study Drug Dose/Route/Schedule:	Aflibercept (8 mg) administered by IVT injection every 4 weeks, followed by dosing interval extension and shortening after week 24 through the week 96 visit, with a minimum dosing interval of 4 weeks.
Procedures and Assessments	Safety and efficacy procedures: ocular examination including BCVA and refraction, intraocular pressure (IOP), slit-lamp examination, indirect ophthalmoscopy, fluorescein angiography (FA), and fundus photography (FP), SD-OCT, ophthalmic exams, vital signs, and evaluating the occurrence of AEs and SAEs.

Statistical Plan	The sample size of approximately 1000 participants (~500 participants with nAMD and ~500 participants with DME) will provide information on safety in these populations. For the primary analysis, participants with at least one ocular TEAE (and serious TEAE) in the study eye and participants with at least one non-ocular TEAE (and serious TEAE) through week 24 will be summarized using descriptive statistics in the SAF population. The SAF population includes all enrolled participants who received at least 1 injection of aflibercept 8 mg during the study. Exploratory efficacy endpoints will be analyzed descriptively.

1. INTRODUCTION

1.1. Background

Chorioretinal vascular disease, including nAMD and DME, are leading causes of vision loss in adults. It is estimated that AMD affects over 196 million people, with nAMD composing 10% of the AMD patient population and affecting 20 million people, worldwide (Wong, 2014) (Flores, 2021). DME, one of the major manifestations of DR, is thought to affect >21 million people, worldwide (Yau, 2012), has a similar global prevalence to nAMD. If left untreated, both conditions will lead to vision loss that can be severe and permanent.

Anti-VEGF drugs have become the standard of care treatment for both these conditions with good success. This approach directly targets VEGF, one of the main mediators of chorioretinal vascular diseases such as DME and nAMD. VEGF is a protein growth factor that both stimulates angiogenesis and increases vascular permeability, playing a key role in the pathophysiology of nAMD and DME (Bhagat, 2009) (Ferrara, 2000) (Nguyen, 2006) (Tan, 2022). In this pathway, hypoxia and other metabolic factors trigger VEGF release, which in turn induces vascular leakage and neovascularization.

Because of its role in the pathology of nAMD and DME, VEGF is an important drug target in treatment strategies. The use of IVT anti-VEGF agents, including aflibercept 2 mg (EYLEA®), for the treatment of nAMD and DME has become the standard of care. Overall, aflibercept has a high-binding affinity for VEGF and PlGF. It neutralizes VEGFR1/R2-mediated biological activity leading to improvement of nAMD and DME.

EYLEA® HD (aflibercept 8 mg, a VEGF antagonist), administered by IVT injection of 70 µL (0.07 mL) at a concentration of 114.3 mg/mL, was approved in the US in Aug 2023 for the treatment of nAMD, DME, and DR. EYLEA HD has also been recently approved for use in the EMA for wet AMD and DME (Jan 2024) (EYLEA HD (aflibercept) [USPI], 2023). The pivotal trials supporting approval, PHOTON (phase 2/3 in DME) and PULSAR (phase 3 in nAMD), demonstrated non-inferiority on the primary efficacy endpoint and a similar safety profile to that of aflibercept 2 mg (EYLEA). These results were achieved at dosing intervals of every 12 to 16 weeks in nAMD and DME (12 weeks in DR). This extended durability reduces the burden of care for patients by reducing the number of injections per year.

While treatments like EYLEA HD allow extended dosing intervals of 8 weeks or longer in the vast majority of patients, there remains a patient population that may still require more frequent dosing, as often as every 4 weeks after the 3 initial monthly doses, either to establish or maintain disease control. A factor in the need for more frequent dosing is likely the individual rate of ocular clearance; in fact, the population PK model has demonstrated that a faster estimated ocular clearance was associated with qualifying for dose interval shortening in PULSAR and PHOTON. The proposed study aims to evaluate the effect of aflibercept 8 mg dosed every 4 weeks in participants with nAMD or DME previously treated with anti-VEGF injections.

Additional background information on the study drug and development program can be found in the IB.

1.2. Disease Background

1.2.1. Neovascular Age-Related Macular Degeneration

AMD is a condition that targets the center of the retina, or the macula, causing central vision loss in older people. It is a leading cause of central vision loss in this population in the developed world (Schmidt-Erfurth, 2007) (Mittra, 2009) (Jager, 2008).

There are 2 clinical subtypes of AMD, broadly described as (i) "dry" AMD and (ii) "wet" or neovascular AMD (wAMD or nAMD) (Jager, 2008) (Hadziahmetovic, 2020). The neovascular form is characterized by retinal edema and neovascular proliferation (Miller, 2013). Although nAMD represents only 10% of the overall prevalence of AMD, it accounts for most AMD related cases of blindness (Jager, 2008) (Bressler, 1987) (Hadziahmetovic, 2020). Vision loss in nAMD results from the VEGF-induced growth of abnormal and fragile blood vessels, termed CNV. These abnormal vessels ultimately leak serous and hemorrhagic fluid in the subretinal space of the macula (Flores, 2021). The fluid disturbs the highly structured architectural arrangement of the photoreceptors causing image distortion and vision loss (Bressler, 1987) (De Jong, 2001).

As observed in clinical trials like the PIER study, undertreatment of nAMD can lead to unrecoverable vision loss that is often unrecoverable even when appropriate treatment is reinstated (Abraham, 2010). Furthermore, this vision loss has serious implications on quality of life and is associated with increased risk of falls, depression, and the need for assistance with daily activities (Cruess, 2007) (Soubrane, 2007).

1.2.2. Diabetic Macular Edema

DME, a common manifestation of DR, is a multifactorial disease characterized by increased permeability of retinal vessels (Aiello, 2005). A hallmark of early diabetic eye disease is the hyperglycemia-induced change in the structure and cellular composition of the retinal microvasculature, particularly endothelial cells and pericytes. Thickening of the basement membrane and reduction in the number of pericytes is believed to lead to increased permeability and incompetence of retinal blood vessels. This compromise of the blood-retinal barrier leads to leakage of plasma constituents into the surrounding retina, resulting in retinal edema and vision loss. This vascular dysregulation also leads to a hypoxic state, which in turn stimulates VEGF production that then furthers microvascular permeability and the retinal edema seen in DME (Aiello, 1994) (Albert D.M, 2000) (Praidou, 2009) (Gündüz, 2007).

As DME develops, central vision becomes blurred or distorted (Antcliff, 1999) (Bringmann, 2004) (Pendergast, 1998). It is the primary cause of vision loss and blindness in patients with diabetes and the most frequent cause of blindness in young and middle-aged adults (Klein, 1984) (Moss, 1994) (Moss, 1998) (Sivaprasad, 2012) (Cheung, 2010). If left untreated, approximately half of patients with DME will lose 2 or more lines of visual acuity within 2 years (Bandello, 2012) (Ciulla, 2003).

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety of aflibercept 8 mg	• Occurrence of TEAEs and serious TEAEs through week 24
Exploratory	
[redacted]	

[redacted]

TEAE=treatment-emergent adverse event, [redacted]

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

No formal hypothesis testing is planned. The study is designed to explore the safety of aflibercept 8 mg dosed every 4 weeks for 24 weeks and will also assess measures of efficacy at week 24 and week 96, following 72 weeks of a "treat-and-extend" dosing regimen.

3.2. Rationale

3.2.1. Rationale for Study Design

There remains an unmet medical need in the treatment of nAMD and DME. Although many patients benefit from treatment with currently available anti-VEGF agents, some patients may still need IVT injections as frequently as every 4 weeks. Due to variability in the severity of disease, factors like ocular clearance rate and response to treatment, some patients require such frequent treatment to establish and/or maintain disease control. Pursuit of an improved treatment paradigm for these patients motivated the development of a high-dose formulation of aflibercept (8 mg; provided at a concentration of 114.3 mg/mL), which has previously been studied in the pivotal trials: PHOTON (phase 2/3 in DME) and PULSAR (phase 3 in nAMD).

In these studies, participants were treated with aflibercept 8 mg at intervals of 12 to 16 weeks (with dosing modification leading to treatment as frequent as every 8 weeks). Among participants with treatment-naïve nAMD enrolled in PULSAR, 79% and 77% were able to maintain a 12- or 16-week treatment interval, respectively, with the aflibercept 8 mg dose while achieving noninferior BCVA results compared to aflibercept 2 mg dosed every 8 weeks. Among participants with treatment-naïve and previously treated DME enrolled in PHOTON, 91% and 89% of participants were able to maintain a 12- or 16-week regimen, respectively, with the 8 mg formulation achieving noninferior BCVA results compared to aflibercept 2 mg dosed every 8 weeks. As the minimum interval in these studies was every 8 weeks, it is likely that some participants would have benefited from even more frequent dosing.

In fact, earlier studies have demonstrated more favorable outcomes with more frequent dosing in a subset of participants. A post-hoc analysis of VIEW1 and VIEW2 showed that participants with nAMD treated with aflibercept 2 mg with 'early persistent fluid' throughout the monthly loading phase (baseline through week 12) gained a mean of 4.2 letters more if randomized to 2q4 compared to those receiving 2q8 (Jaffe, 2016). These results indicate that participants with nAMD with incomplete treatment responses during the initial monthly dosing phase fare better with continued more frequent dosing. Studies have shown similar trends in participants with DME. The results of the DRCR-run Protocol T study that allowed for dosing based on disease activity (following initial monthly doses), comparing multiple anti-VEGF therapies, showed that many participants with DME also require frequent dosing, eg, every 4 weeks, to improve or maintain functional and anatomical outcomes (Wells, 2016).

In either disease, lost vision may not be regained, even with subsequent increases in treatment frequency. Furthermore, insufficient treatment frequency may result in a patient's vision deteriorating below certain thresholds that would preclude many activities of daily living, including driving and reading. It is therefore critical to treat patients adequately and to increase the frequency of dosing when there is a need, ie, when persistent or recurrent disease activity is noted.

The proposed study aims to evaluate the safety and measures of efficacy of aflibercept 8 mg dosed every 4 weeks in participants already receiving treatment for nAMD or DME with standard of care anti-VEGF agents. Additionally, this study will explore the ability for participants to achieve anatomic control with monthly dosing such that it is possible to extend the dosing interval after week 24.

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 for Aflibercept

Aflibercept 2 mg is marketed for the treatment of patients with several retinal diseases that are characterized by up-regulation of VEGF, are related to pathological neo-vascularization and/or vascular leakage, and can result in retinal thickening and edema, which is thought to contribute to vision loss. Aflibercept 8 mg is also approved for nAMD and DME in the US, to be dosed every 4 weeks for the first 3 doses, followed by dosing via IVT injection once every 8 to 16 weeks. Aflibercept 8 mg for IVT injection is approved for DR in the US to be dosed every 4 weeks for the first 3 months, followed by dosing via IVT injection once every 8 to 12 weeks (EYLEA HD (aflibercept) [USPI], 2023).

The safety profile of the aflibercept 2 mg formulation has been thoroughly investigated in a comprehensive clinical study program in the indications of nAMD, CRVO, BRVO, mCNV, DME, and DR in adults; and ROP in preterm infants. As of Feb 2023, more than 4,954 participants have been treated with aflibercept 2 mg in clinical studies. Participants were treated for up to 148 weeks with aflibercept during these studies. No new safety findings were observed with long-term treatment with aflibercept.

The efficacy and safety of aflibercept 8 mg have been studied in the ongoing pivotal studies, PHOTON and PULSAR, and as of Feb 2023, more than 1,217 participants have been treated with aflibercept 8 mg. The safety profile of aflibercept 8 mg in these studies were consistent with the known safety profile of aflibercept 2 mg. No new safety signals were observed. Intraocular inflammation, retinal tear/detachment, transient increase in IOP, traumatic cataract, hypersensitivity, and immunogenicity are important identified risks for aflibercept.

Important potential risks include ATEs and embryo-fetotoxicity. The important potential risk of ATEs has been associated with the systemic administration of anti-VEGF medications. However, to date, no causal association of locally administered IVT aflibercept 2 mg or 8 mg and the development of ATEs was identified. The important potential risk of embryo-fetotoxicity is based on preclinical testing with extremely high doses of aflibercept administered to animals (by far exceeding the doses which would be given to humans).

More detailed information about the known and expected benefits and risks of aflibercept may be found in the IB.

3.3.1. Study Conduct in Response to Unforeseen Circumstances

Recognizing that an event of unforeseen circumstances, eg, COVID-19 restrictions/ national/international emergencies may have an impact on the conduct of clinical trials, the sponsor does not intend to screen any participants at the affected site(s) until the impact of the emergency is deemed manageable and no longer interfering with the conduct of studies at site(s), and participants can safely participate in this study.

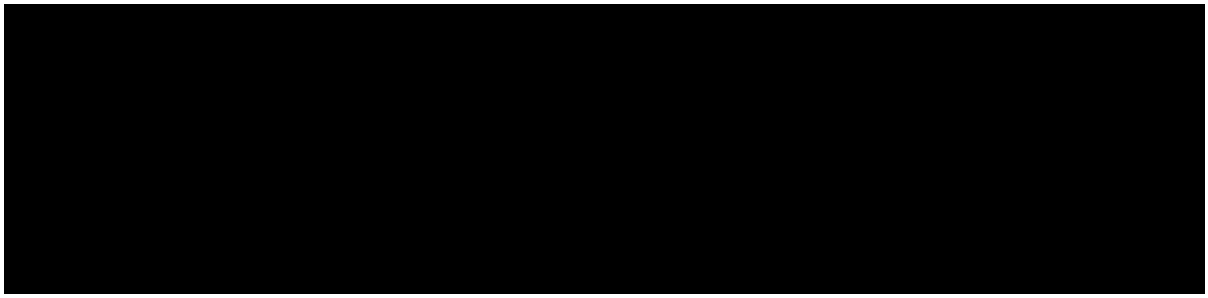
The continuity of clinical study conduct dictated by the SOE (Table 2) and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Any study data collected using an alternative mechanism will be documented.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, and gender), disease characteristics (eg, baseline BCVA), medical history, and medication history for each participant.

4.2. Safety and Efficacy Variables



5. STUDY DESIGN

5.1. Study Description and Duration

This is a phase 3b, multicenter, single-arm study to assess the safety and measures of efficacy of treatment with aflibercept 8q4 in participants with nAMD or DME previously treated with IVT anti-VEGF injections.

This study consists of a screening/enrollment visit, a treatment period, and an EOS visit at week 96.

Eligibility will be assessed at the screening visit on day 1. Participants with nAMD or DME are eligible for screening if they have been previously treated with ≥3 anti-VEGF injections over the prior 5 months (~150 days). Approximately 1000 participants (~500 participants with nAMD and ~500 participants with DME) who meet all eligibility criteria will be enrolled.

The screening visit should be held approximately 4 to 7 weeks (25 to 49 days) after the most recent anti-VEGF injection and, for eligible participants, the initial study treatment will occur on the same day. Participants will receive a total of 7 injections of aflibercept 8q4, from baseline through week 24.

To assess the ability to extend dosing intervals with aflibercept 8 mg in this population, Dose Regimen Modification (DRM) criteria will be used to assess potential dose interval extensions, as well as subsequent dose interval shortening at each visit beginning at week 24. The minimum interval between injections is 4 weeks (28 days).

Dose Regimen Modification Criteria for Extension (DRM-E):

Beginning at week 24, if DRM criteria for extension (DRM-E) are met, the interval between consecutive injections will be extended following a "treat-and-extend" paradigm. Dose intervals will be extended by 2 weeks when DRM-E criteria are met at any Dosing visit as long as the dose interval has not been shortened previously. For participants who have had their dose interval shortened previously, the dose interval will only be extended by 1 week increments and only after a minimum of 12 weeks (84 days) has passed.

Participants will be eligible for interval extension if the following criteria are met at **any Dosing visit**:

nAMD

- No retinal fluid in central subfield

  AND

- No new onset foveal neovascularization or foveal hemorrhage

  AND

- No interval shortening within the last 12 weeks (84 days)

DME

- CST <300 µm [redacted]

  AND

- ≤10 µm increase (worsening) from lowest (best) previous CST value

AND

- No interval shortening within the last 12 weeks (84 days)

Dose Regimen Modification Criteria for Shortening (DRM-S)

If a participant's interval has been extended, then the dose interval may be shortened by 1 week if the DRM-S criteria are met. If the DRM-S criteria are met at either a dosing or a non-dosing visit, the participant will be dosed, and the subsequent interval will be shortened to the time from the most recent dose minus 1 week. The minimum interval between injections will be 4 weeks (q4).

Participants will be eligible for interval shortening (by 1-week increments), if one of the following criteria are met at **any scheduled visit**:

nAMD

- Any new retinal fluid in central subfield

OR

- New onset foveal neovascularization or foveal hemorrhage

OR

- >5 letter loss in BCVA from best previous attributable to recurrent or persistent disease

DME

- >25 µm increase in CST from previous visit

OR

- >10 letter loss in BCVA from best previous attributable to recurrent or persistent disease

DRM-E and DRM-S criteria will be assessed by the investigator. Participants who do not meet the above criteria for interval extension or shortening at a given visit will continue treatment at the current interval.

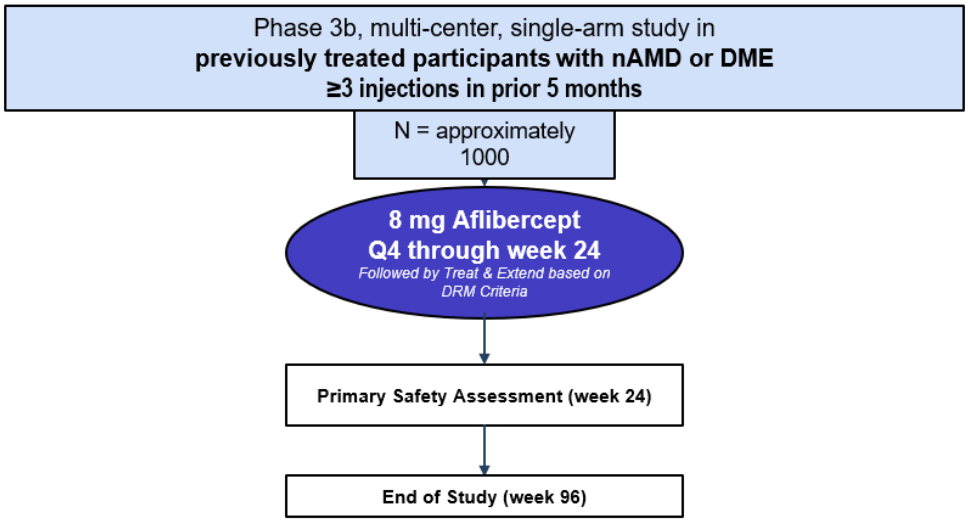
Participants will be seen every 4 weeks through week 24. After week 24, participants will return for Dosing visits scheduled based on their DRM assessments. Dosing visits should be scheduled as close to the planned date as possible. Mandatory visits will occur approximately every 12 weeks through the EOS visit for all participants, regardless of dosing schedule (refer to the SOE, Table 2). Mandatory visits can be moved to within the ±17-day visit window to be combined with Dosing visits when the visit windows overlap (except visit 13, week 96). Participants may be seen for unscheduled visits at the investigator's discretion at any time.

The primary analysis will occur once all participants have completed week 24 (or prematurely discontinued), with the final analysis occurring after all participants have completed the study at week 96 (or prematurely discontinued). Additional analyses may be performed at other timepoints, eg, week 48.

Safety will be assessed by ophthalmic exams, collection of vital signs (including HR and BP), and by evaluating the occurrence of AEs and SAEs. All AEs reported in this study will be coded using the MedDRA®.

The study flow diagram and dosing schedules are presented in Figure 1 and Figure 2.

Figure 1: Study Flow Diagram



Q4=once every 4 weeks, DME=diabetic macular edema, DRM=dose regimen modification, nAMD=neovascular age-related macular degeneration

Figure 2: Dosing Schedule

	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 ↓	Dosing Wks 28 to 35	Mand Wk 36	Dosing Wks 37 to 47	Mand Wk 48	Dosing Wks 49 to 59	Mand Wk 60	Dosing Wks 61 to 71	Mand Wk 72	Dosing Wks 73 to 83	Mand Wk 84	Dosing Wks 85 to 95	Mand Wk 96 EOS
8mg	X	X	X	X	X	X	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	

*Participants will be evaluated for interval modification based on DRM criteria beginning at week 24.
EOS=end of study, Mand=mandatory, ↓= primary safety assessment, wk(s)=weeks

5.1.1. End of Study Definition

The EOS is defined as the last visit of the last participant in the study.

5.2. Planned Interim Analysis

No interim analysis is planned.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PARTICIPANTS

6.1. Number of Participants Planned

It is estimated that approximately 1000 participants will be enrolled in this study (approximately 500 participants with nAMD and approximately 500 participants with DME).

6.2. Study Population

6.2.1. Participant Population

The study population will consist of male and female participants with nAMD (age ≥50 years) or DME (age ≥18 years) previously treated with anti-VEGF injections.

6.2.2. Study Eye Population

Only 1 eye per participant will be enrolled as the study eye. For participants who meet eligibility criteria in both eyes, the eye that is expected to require more frequent treatment should be chosen as the study eye based on investigator discretion. The study eye selection will be decided based on the investigator's discretion at baseline and must not be changed during the course of the study. The non-study eye is then considered as the "fellow eye."

6.2.3. Inclusion Criteria

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

Inclusion Criteria for Participants with nAMD

1. Men or women ≥50 years of age
2. History of CNV lesions secondary to nAMD in the study eye, requiring continued anti-VEGF treatment, as determined by the investigator. Participants with polypoidal choroidal vasculopathy or retinal angiomatous proliferation in the study eye are eligible to participate in the study, and their condition should be documented.
3. Criterion removed in Amendment 1

Inclusion Criteria for Participants with DME

4. Men or women ≥18 years of age
5. History of DME with central involvement (in the central subfield on SD-OCT) in the study eye, requiring continued anti-VEGF treatment, as determined by the investigator

Inclusion Criteria for All Participants

6. Previously treated with ≥3 anti-VEGF IVT injections in the study eye in the 5 months (~150 days) prior to visit 1
7. History of response to anti-VEGF IVT injections in the study eye such that continued treatment is warranted in the investigator's opinion
8. Willing and able to comply with clinic visits and study-related procedures

9. Provide informed consent signed by study participant

6.2.4. Exclusion Criteria

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

Exclusion Criteria for Participants with nAMD

1. Evidence of CNV due to any cause other than nAMD in either eye
2. Subretinal hemorrhage in the study eye ≥~50% of the total lesion area per investigator
3. DME or DR, defined in the diabetic participants with nAMD as DR lesions in the assessable area of the retina in the study eye

Exclusion Criteria for Participants with DME

4. Evidence of macular edema due to any other cause other than diabetes mellitus in the study eye
5. Advanced age-related macular degeneration (nAMD or geographic atrophy) in the study eye
6. Active proliferative DR in the study eye
7. PRP or macular laser photocoagulation in the study eye within 12 weeks (84 days) of visit 1

Exclusion Criteria for All Participants

8. Prior IVT investigational agents in study eye
9. Prior IVT investigational agents in fellow eye
10. Prior treatment with pegcetacoplan injection or avacincaptad pegol injection at any time in the study eye
11. Criterion removed in Amendment 1
12. Prior treatment with gene therapy and/or cell therapy in the study eye
13. Prior treatment with gene therapy and/or cell therapy in the fellow eye
14. Use of topical steroids in the study eye within 4 weeks (28 days) of visit 1
15. Previous use of intraocular or periocular corticosteroids in the study eye within 120 days of visit 1
16. Use of any IVT implantable agents (eg, Iluvien®, Ozurdex®, Susvimo®) at any time in the study eye
17. Treatment with ocriplasmin in the study eye at any time
18. YAG capsulotomy in the study eye within 14 days of visit 1
19. History of vitreoretinal surgery (including scleral buckling) in the study eye
20. Any other intraocular surgery in the study eye within 12 weeks (84 days) of visit 1
21. IOP ≥25 mm Hg in the study eye
22. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in study eye

23. Any intraocular inflammation/infection in study eye within 90 days of visit 1
24. Any intraocular inflammation/infection in fellow eye within 90 days of visit 1
25. Any history of macular hole of stage 2 and above in the study eye
26. Concurrent disease that causes substantial decrease of BCVA, is expected to limit BCVA recovery, or is likely to require medical or surgical intervention during the study in the study eye
27. Structural damage in the study eye that is likely to preclude improvement in BCVA following the resolution of macular edema (eg, atrophy of the retinal pigment epithelium, preretinal fibrosis, subretinal fibrosis or scar, significant macular ischemia, or organized hard exudates)
28. Current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment visible in the study eye
29. Inability to perform ophthalmic exams, obtain fundus photographs, FA, or OCT (eg, due to media opacity, allergy to fluorescein dye or lack of venous access) in the study eye
30. History of corneal transplant in the study eye
31. Any corneal dystrophy affecting the visual axis in the study eye based on investigator assessment
32. Aphakia, or pseudophakia with absence of posterior capsule (unless it occurred as a result of a YAG posterior capsulotomy) in the study eye
33. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the participant beyond what is to be expected from standard procedures of IVT injections, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety
34. Any prior systemic anti-VEGF administration
35. Uncontrolled BP (defined as systolic >140 mm Hg or diastolic >90 mm Hg)
36. History of cerebrovascular accident or myocardial infarction within 180 days of visit 1
37. Renal failure, dialysis, or history of renal transplant
38. Known sensitivity to any of the compounds of the study formulation
39. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the participant at high risk for treatment complications
40. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor
41. Participation in an investigational study within 30 days prior to screening visit that involved treatment with any drug (excluding vitamins and minerals) or device
42. Pregnant or breastfeeding women.

43. Men and 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. IUD; 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†,‡.

    Pregnancy testing and contraception are required for WOCBP. Pregnancy testing and contraception are not required for women who are post-menopausal or permanently sterile.

    *WOCBP are defined as women who are fertile following menarche until becoming post-menopausal, 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 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 CTFG guidance. Pregnancy testing and contraception are not required for women with documents hysterectomy or tubal ligation.

    **Vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participants) or vasectomized study participants 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 participant.

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

6.3. Premature Withdrawal from the Study

A participant 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 participant from the study if it is no longer in the interest of the participant to continue in the study, or if the participant's continuation in the study places the scientific outcome of the study at risk (eg, if a participant does not or cannot

follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of participant should be avoided.

Participants who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 8.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.3.2.

6.4. Replacement of Participants

Participants prematurely discontinued from study/study drug will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Instructions on dose preparation are provided in the pharmacy manual. Aflibercept will be provided as a single-use glass vial designed to provide 8 mg (0.07 mL of 114.3 mg/mL solution) for IVT injection. See Table 1 for details.

Table 1: Study Intervention Administered

Intervention Label	**Aflibercept**
Intervention Name	Aflibercept 8 mg
Intervention Description	IVT injection
Type	Biologic
Dose Formulation	Liquid formulation
Unit Dose Strength(s)	114.3 mg/mL
Dosage Level(s)	8 mg (70 µL)
Route of Administration	IVT
Frequency	Every 4 weeks through week 24, followed by "treat-and-extend" based on DRM criteria.
Use	Experimental
IMP	IMP
Sourcing	Provided centrally by the sponsor

IMP=Investigational Medicinal Product; IVT=Intravitreal

Fellow eye treatment will be allowed with aflibercept 8 mg at the investigator's discretion and supplied through IWRS. The treated fellow eye will not be considered an additional study eye.

7.2. Rescue Treatment(s)

There is no alternative rescue treatment defined for this study.

7.3. Dosing Modifications and Study Treatment Discontinuation Rules

7.3.1. Dosing Modifications

Concentrations/volumes of the drug used in the study will not be modified for an individual participant outside that described in the protocol.

7.3.2. Study and Study Drug Discontinuation

A participant may withdraw from study treatment or the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

Participants must be withdrawn if any of the following occurs:

- Relevant SAE(s) if the sponsor or investigator sees this as medical reason to warrant withdrawal
- An AE (ocular or non-ocular) that, from the participant's or the investigator's view, is severe enough to require withdrawal from the study. The investigator must notify the sponsor immediately if a participant is withdrawn because of an AE/SAE
- At the discretion of the treating investigator. The development of conditions which would have prevented a participant's entry into the study according to the selection criteria is no reason per se for withdrawal. However, the withdrawal in such cases remains at the discretion of the treating investigator
- Decision by the investigator or sponsor that termination is in the participant's best medical interest or administrative decision for a reason other than an AE/SAE
- A female participant becomes pregnant (see Section 9.1.3)
- Lost to follow-up
- Decision by the sponsor to halt the entire study

Participants may be withdrawn if any of the following occurs:

- If any treatment for nAMD or DME other than study drug is given in the study eye
- If systemic anti-angiogenic agents are taken by the participant during the study
- If, in the investigator's opinion, continuation in the study would be harmful to the participant's well-being
- At the specific request of the sponsor and in liaison with the investigator (eg, obvious noncompliance or safety concerns)

Participants who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Participants who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.2.

7.4. Method of Treatment Assignment

All participants are assigned to aflibercept 8 mg in this single-arm study.

7.5. Masking

Not applicable, as this is a single-arm study.

7.6. Treatment Logistics and Accountability

7.6.1. Packaging, Labeling, and Storage

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.

7.6.2. Supply and Disposition of Treatments

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

7.6.3. Treatment Accountability

All drug accountability records must be kept current.

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

- dispensed to each participant
- 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; copies must be provided to the sponsor at the conclusion of the study.

7.6.4. Treatment Compliance

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

7.7. 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.

7.7.1. Prohibited Medications and Procedures

Study Eye:

Participants are not allowed to receive any standard or investigational treatments or procedures for nAMD and DME in the study eye other than their assigned study treatment with aflibercept 8 mg as specified in this protocol until they have completed the EOS/early discontinuation visit assessments. This includes medications or procedures administered locally (eg, IVT agents, juxtascleral, or periorbital routes), as well as those administered systemically with the intent of treating nAMD or DME in the study eye. Additionally, participants are not allowed to receive any standard or investigational treatments or procedures for dry AMD, including geographic atrophy, in the study eye.

Fellow Eye:

Aflibercept 8 mg will be allowed for treatment of the fellow eye at the discretion of the investigator and will be supplied through the IWRS. Participants should not receive any other anti-VEGF agent

in the fellow eye. Additionally, participants are not allowed to receive any standard or investigational treatments or procedures for dry AMD, including geographic atrophy, in the fellow eye. The only exception is approved anti-complement IVT treatments (pegcetacoplan and avacincaptad pegol) that was initiated in the fellow eye prior to study start.

7.7.2. Permitted Medications and Procedures

Any other medications or procedures that are considered necessary for the participant's welfare, and that are not expected to interfere with the evaluation of the study treatments, are allowed.

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 2.

Table 2: Schedule of Events

Study Procedure	Visit 1 Screening/Baseline Treatment[1]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[2]	Dosing Visits[2] (Based on DRM)	Mandatory Visit 8	Dosing Visits[2] (Based on DRM)	Mandatory Visit 9	Dosing Visits[2] (Based on DRM)	Mandatory Visit 10	Dosing Visits[2] (Based on DRM)	Mandatory Visit 11	Dosing Visits[2] (Based on DRM)	Mandatory Visit 12	Dosing Visits[2] (Based on DRM)	EOS Mandatory Visit 13[12]
Week(s)	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28-35**	**36[2,3]**	**37-47**	**48[2,3]**	**49-59**	**60[2,3]**	**61-71**	**72[2,3]**	**73-83**	**84[2,3]**	**85-95**	**96**
Study Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197-246**	**253**	**260-330**	**337**	**344-414**	**421**	**428-498**	**505**	**512-582**	**589**	**596-666**	**673**
Window (days)		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±3**	**±17**	**±3**	**±17**	**±3**	**±17**	**±3**	**±17**	**±3**	**±17**	**±3**	**±5**
Informed Consent (ICF)	X																		
Inclusion/ Exclusion	X																		
Medical History	X																		
Demographics	X																		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DRM Assessment[2]							X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration[4]	X	X	X	X	X	X	X	X[2]	X[2, 3]	X[2]	X[2,3]	X[2]	X[2,3]	X[2]	X[2,3]	X[2]	X[2,3]	X[2]	
BCVA/ refraction[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit-lamp exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FA, FP[8]	X			X			X				X								X
SD-OCT[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	**Visit 1** Screening/Baseline Treatment[1]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7[2]**	**Dosing Visits[2]** (Based on DRM)	**Mandatory Visit 8**	**Dosing Visits[2]** (Based on DRM)	**Mandatory Visit 9**	**Dosing Visits[2]** (Based on DRM)	**Mandatory Visit 10**	**Dosing Visits[2]** (Based on DRM)	**Mandatory Visit 11**	**Dosing Visits[2]** (Based on DRM)	**Mandatory Visit 12**	**Dosing Visits[2]** (Based on DRM)	**EOS Mandatory Visit 13[12]**
Week(s)	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28-35**	**36[2,3]**	**37-47**	**48[2,3]**	**49-59**	**60[2,3]**	**61-71**	**72[2,3]**	**73-83**	**84[2,3]**	**85-95**	**96**
Study Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197-246**	**253**	**260-330**	**337**	**344-414**	**421**	**428-498**	**505**	**512-582**	**589**	**596-666**	**673**
Window (days)		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±3**	**±17**	**±3**	**±17**	**±3**	**±17**	**±3**	**±17**	**±3**	**±17**	**±3**	**±5**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[11] (Urine only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

BCVA=best-corrected visual acuity, DRM=dose regimen modification, FA=fluorescein angiography, FP=fundus photography, ICF=informed consent form, IOP=intraocular pressure, SD-OCT=spectral domain optical coherence tomography

8.1.1. Footnotes for the Schedule of Events Table

1. Participants who meet all eligibility criteria will be treated on the same day. Screening should take place approximately 4 to 7 weeks (25 to 49 days) after the last treatment.
2. Participants' study eye will be assessed based on DRM criteria starting at week 24. If DRM criteria are met, the participant will be dosed at that visit and the next dose will be given at the updated interval (see Section 5.1). Subsequently, Dosing visits will be scheduled as needed based on an individual participant's dosing interval, as determined by DRM assessments. Dosing visits should be scheduled as close to the planned dosing date as possible and will be combined with Mandatory visits as appropriate; it is expected that participants only complete the visits that coincide with their dosing schedule and the Mandatory visits (see footnote #3). In addition to Dosing visits listed in the SOE, Dosing visits (±3 days) may also occur at weeks 36, 48, 60, 72, and 84, directly coinciding with a Mandatory visit.
3. Participants will return at least every 12 weeks for Mandatory visits, regardless of whether a dose is required at that visit. However, whenever possible, the Mandatory visits (except visit 13, week 96) should be moved to be combined with a Dosing visit if the Dosing visit is scheduled 1) at the same time point, 2) 1 or 2 weeks before, or 3) 1 or 2 weeks after, given that the visit window for the Mandatory visit is ±17 days. If a participant is scheduled for both a Dosing visit 2 weeks before AND 2 weeks after a Mandatory visit, the Mandatory visit should be conducted with the earlier Dosing visit, when possible.
4. Refer to pharmacy manual for study drug injection guidelines. Following study drug injection, participants will be observed for approximately 30 minutes.
5. [redacted]
6. IOP will be measured at all study visits (bilaterally). On days when the study drug is administered, IOP should be measured pre-dose (bilaterally) and approximately 30 minutes after administration of study drug (study eye only). IOP will be measured using applanation tonometry (eg, Goldmann applanation tonometry, Perkins tonometer), combined applanation and indentation (eg, Tono-pen®), or rebound tonometry (eg, Icare), and the same method of measurement must be used in each participant throughout the study.
7. Indirect ophthalmoscopy will be performed pre-dose bilaterally at all visits. On days when study drug is administered, it should also be performed immediately after administration of study drug (study eye only).
8. FA and FP should be performed prior to administration of study drug, when applicable. For FA, the study eye will be the transit eye and images should be collected using the widest field available. Sites may submit ultra-widefield color photographs instead of FP for DME participants. If submitting FP images on DME participants, and ultra-widefield equipment is available, sites should also submit an optional ultra-widefield color photograph.
9. Wherever possible, the same SD-OCT imaging system should be used at all study visits in each participant. Images will be taken in both eyes before dosing at each required visit.

10. Vital signs (HR and BP) should be measured pre-injection. When possible, BP assessments will be taken using AOBP with the Microlife WatchBP Office AFIB BP device (or comparable). BP assessments will be taken by the device in triplicate and a mean measure as displayed will be recorded in the EDC.
11. For WOCBP, a negative urine pregnancy test at screening is required for eligibility and before treatment is administered in either eye at subsequent visits.
12. The EOS visit (visit 13, week 96) cannot be combined with a Dosing visit. This visit will also represent the early termination visit.

8.1.2. Early Termination Visit

Participants who are withdrawn from the study will be asked to return to the clinic once for an early termination visit consisting of the EOS assessments described in Table 2.

8.1.3. Unscheduled Visits

All attempts should be made to keep participants 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. Ocular Study Procedures (Safety and Efficacy)

8.2.1.1. Best-Corrected Visual Acuity

Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (ETDRS Research Group, 1985) at 4 meters at each study visit specified in Table 2.

VA examiners must be certified to ensure consistent measurement of BCVA. BCVA should be assessed before any other ocular procedures are performed.

[redacted]

8.2.1.2. Intraocular Pressure

IOP of the study eye will be measured in both eyes at every visit using applanation tonometry (eg, Goldmann applanation tonometry, Perkins tonometer), combined applanation and indentation (eg, Tono-pen®), or rebound tonometry (eg, Icare), as specified in Table 2. The same method of IOP measurement must be used throughout the study for each individual participant. IOP will be measured pre-dose (bilaterally) and at approximately 30 minutes post-dose (study eye only).

8.2.1.3. Slit-Lamp Examination

Participants' anterior eye structure and ocular adnexa will be examined bilaterally pre-dose at each study visit using a slit lamp by the investigator, as specified in Table 2.

8.2.1.4. Indirect Ophthalmoscopy

Participants' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre-dose (bilateral) and post-dose (study eye only), as specified in Table 2. Post-dose evaluation must be performed immediately after injection.

8.2.1.5. Fluorescein Angiography/Fundus Photography

The anatomical state of the retinal vasculature, including leakage and perfusion status will be evaluated by FP and FA pre-dose in the study eye as specified in Table 2. FP and FA will be captured and transmitted to an independent reading center for both eyes. For FA, the study eye will be the transit eye and images should be collected using the widest field available. Sites may submit ultra-widefield color photographs instead of FP for DME participants. If submitting FP images on DME participants, and ultra-widefield equipment is available, sites should also submit an optional ultra-widefield color photograph.

Fundus and angiographic images will be sent to an independent reading center. Details on independent reading procedures can be found in a separate charter provided by the reading center. All FP and FA images will be archived at the site as part of the source documentation. Photographers must be certified by the reading center to ensure consistency and quality in image acquisition.

Detailed instructions on imaging collection are in the Imaging manual provided to study sites.

8.2.1.6. Spectral Domain Optical Coherence Tomography

Retinal characteristics will be evaluated at each study visit using SD-OCT as specified in Table 2. Images will be captured and transmitted for both eyes. Images will be taken in both eyes before dosing at each required visit. Images will be sent to an independent reading center. All OCTs will be electronically archived at the study site as part of the source documentation. OCT technicians must be certified by the reading center to ensure consistency and quality in image acquisition.

Detailed instructions on imaging collection are in the Imaging manual provided to study sites.

8.2.2. Safety Procedures (Non-Ocular)

8.2.2.1. Vital Signs

Vital signs (HR and BP) will be collected pre-dose at all visits as specified in Table 2.

When possible, BP assessments will be taken using an AOBP with the Microlife WatchBP Office AFIB BP device (or comparable). BP assessments will be taken by the device in triplicate and a mean measure as displayed will be recorded in the EDC.

8.2.2.2. Laboratory Testing

Urine pregnancy tests will be performed for all WOCBP at every treatment visit, and a negative result must be documented before study eye treatment or fellow eye treatment can be administered.

9. SAFETY EVALUATION AND REPORTING

9.1. Recording and Reporting Adverse Events

9.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the ICF to the end of study. Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the participant. AEs may be directly observed, reported spontaneously by the participant, or by questioning the participant at each study visit. Participants 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 9.2. 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. Isolated vital sign findings or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the 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 9.2 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 study) 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 Sections 9.1.2 and 9.1.3.

9.1.2. Reporting Procedure

9.1.2.1. Individual Case Safety Reporting

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. All SAEs must be reported to the sponsor (or designee) by completing the AE CRF immediately, but no later than 24 hours of learning of the event. For SAEs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF and retained at the study center and available upon request.

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

9.1.3. 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** 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 120 days (4 months) of the last dose of study drug. Any complication of pregnancy affecting a female study participant or female partner of a male study participant, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. The outcome for all pregnancies should be reported to the sponsor.

9.2. Definitions

9.2.1. Adverse Event

An AE is any untoward medical occurrence in a participant 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, symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH, 1994).

9.2.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a participant is a passenger).
- Is **life-threatening** – in the view of the investigator, the participant 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 participant 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

An ocular important medical event may include the following:

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

Criteria for reporting SAEs must be followed for these events.

9.2.3. Severity

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

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

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptoms may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the participant's health. Treatment for symptoms may be given and/or participant hospitalized.

9.2.4. Causality

The investigator must provide a 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 and 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
- Participant'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, participant'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, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the Injection Procedure

The relationship of AEs to the injection procedure will be assessed by the investigator, and is 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:

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

Causality to the other protocol-specified procedures (excluding injection 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, participant's clinical condition (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, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

9.3. Safety Monitoring

The investigator will monitor the safety of study participants at his/her site(s) as per the requirements of this protocol and consistent with current 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 Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, 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.

Additionally, safety oversight will be provided by an internal SMT. The SMT is a cross-functional team that meets on a periodic basis to monitor the safety profile of the study product, to identify safety signals in a timely fashion, and to initiate an appropriate plan of action.

9.4. Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, IRBs, and the participating investigators of any SUSARs occurring in other study centers or other studies of the active study drug (aflibercept), as appropriate per applicable reporting requirements, including Regulation EU No. 536/2014. 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 the study drug, aflibercept, is assessed against the Reference Safety Information section of the IB 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 CSR to health authorities and IRBs as appropriate.

10. STATISTICAL PLAN

This is a single-arm study; only descriptive statistics will be reported. The primary analysis for this study will be performed once all participants have completed week 24 (or prematurely discontinued).

Because only descriptive statistics will be reported for this study, analyses may be performed as necessary at additional timepoints, eg, week 48.

10.1. Statistical Hypothesis

There is no formal statistical hypothesis in this study.

10.2. Justification of Sample Size

The sample size of approximately 1000 participants (~500 participants with nAMD and ~500 participants with DME), will provide information on safety in these populations.

10.3. Analysis Sets

10.3.1. Safety Analysis Set

The SAF population includes all enrolled participants who received at least 1 injection of aflibercept 8 mg during the study. Treatment compliance, administration/exposure, efficacy endpoints, and 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 participants reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

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

10.4.1. Participant Disposition

The number and percentage of participants screened, enrolled, and the primary reasons for screening failure and discontinuation will be summarized.

10.4.2. Demography and Baseline Characteristics

Demographic variables (eg, age, race, and gender), baseline characteristics, medical history, and prior and concomitant medications and therapies will be summarized.

10.4.3. Analyses

10.4.3.1. Primary Analysis

For the primary analysis, participants with at least one ocular TEAE (and serious TEAE) in the study eye and participants with at least one non-ocular TEAE (and serious TEAE) through week 24 will be summarized using descriptive statistics in the SAF population.

10.4.3.2. Exploratory Analysis

[redacted]

10.4.4. Control of Multiplicity

No multiplicity adjustments are required for this study.

10.4.5. Safety Analysis

10.4.5.1. Adverse Events

TEAEs are defined as those AEs with either initial onset after the first dose of study treatment or that worsen after the first dose of study treatment.

For the week 24 primary analysis period, the TEAEs will be summarized to the last dose of study drug plus 30 days or the week 24 visit, whichever is later. For the entire study period, the TEAEs will be summarized to the last dose of study drug plus 30 days or the end of study, whichever is later.

The number (n) and percentage (%) of participants who reported any of the following will be summarized:

- Overview of TEAEs
- TEAEs by primary SOC and PT
- TEAEs by primary SOC, PT, and maximum severity
- Treatment-related TEAEs by primary SOC and PT
- Serious TEAEs by primary SOC and PT
- TEAEs leading to study treatment discontinuation will be listed and summarized
- Deaths will be listed and summarized

10.4.5.2. Other Safety

Vital Signs

Vital signs (HR and BP) and their changes from baseline to each scheduled assessment time will be summarized by visit with descriptive statistics.

Intraocular Pressure

Pre-dose IOP measurements and changes from baseline will be summarized by visit using descriptive statistics for the study eye. Post-dose IOP measurements and changes from baseline will be summarized for the study eye. The proportion of participants who meet the following criteria will be summarized descriptively:

- ≥10 mm Hg increase in IOP measurement from baseline to pre-dose measurement in the study eye (by visit and at any time)
- ≥25 mm Hg for any pre-dose measurement in the study eye (by visit and at any time)

- ≥35 mm Hg at any time (pre- or post-dose) in the study eye (by visit and at any time)

10.4.5.3. Treatment Exposure

The total number of injections administered to each participant during the study and the duration of treatment will be summarized using descriptive statistics in the SAF population. Additionally, the proportion of participants treated at various intervals after week 24 will be summarized.

10.4.5.4. Treatment Compliance

Compliance during the week 24 period with protocol-defined study medication will be calculated as follows:

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

10.5. Interim Analysis

No interim analysis is planned.

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. The investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 14.1.

11. 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), including Regulation EU No. 536/2014. The planned quality assurance and quality control procedures for the study are described in this section.

11.1. Data Management and Electronic Systems

11.1.1. Data Management

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

AEs and medical history will be coded using MedDRA. A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history/ophthalmic history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an EDC, [redacted].

11.1.2. Electronic Systems

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

- IWRS system – study drug supply
- EDC system – data capture – [redacted]
- SAS – statistical review and analysis
- Pharmacovigilance safety database

11.2. Study Monitoring

11.2.1. 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 ICH E6 (R2) Guideline for Good Clinical Practice. 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 may include reduced SDV, targeted SDR, the use of onsite and remote monitoring visits (as allowed by local laws), and Centralized Monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

The study monitors may perform targeted SDR to verify that data recorded in the CRF by authorized site personnel are accurate and verifiable from source documents, that the safety and rights of participants 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.

11.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate participant records (source documents). The site is responsible to ensure quality within their records and systems and is 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. Electronic CRFs and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.2.3. Case Report Form Requirements

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

11.3. Audits and Inspections

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

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

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

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

11.4. Study Documentation

11.4.1. Certification of Accuracy of Data

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

11.4.2. 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.

11.4.3. Recruitment Strategy

Potential study participants may be identified by the investigator through a variety of means, such as publicizing the study or using existing participant lists. Recruitment resources may include, but are not limited to, recruitment flyers, brochures, social media ads, newspaper ads, radio ads, etc. A third-party vendor may assist in recruitment efforts, such as the development of recruitment materials. All participant-facing recruitment material, including media advertising and receptionist scripts, will be reviewed and approved by the appropriate IRB/authority prior to use. Resources may be in paper or electronic form. Regeneron will not access any participant identifiable information as part of recruitment efforts.

11.4.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities
- The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches; and respective communication and cooperation of the parties

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. 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.

12.2. Informed Consent

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

An ICF can be defined as either a paper consent form or an electronically-delivered consent (eConsent). An eConsent may be provided only where allowable by local laws and regulations and by site policies.

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 participant 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 participant in language that he/she can understand. The ICF should be signed and dated by the participant and by the investigator or authorized designee who reviewed the ICF with the participant.

- Participants who can write but cannot read will have the ICF read to them before signing and dating the ICF
- Participants 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 participant's study record, and a copy of the signed ICF must be given to the participant.

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 participants 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 participant's study record and a copy must be given to the participant.

12.3. Participants Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study participant will be maintained. Participants should be identified by a participant 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 participant'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.

12.4. Institutional Review Board/Ethics Committee

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 participants (eg, advertising) before any participant 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 participant, 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 participants 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.

12.5. Clinical Study Data Transparency

Final study results will be published on public clinical trial registries according to applicable local guidelines and regulations. For data integrity, scientific, and statistical reasons, published results from all participants will be disclosed following the EOS (Section 5.1.1).

Treatment codes will be disseminated to each investigation site thereafter.

13. 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.

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

14.1. 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.

14.2. 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 participant 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 guideline
- The total number of participants 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 participants' interests.

15. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

16. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

17. PUBLICATION POLICY

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

18. REFERENCES

Abraham P, Yue H, Wilson L. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2. American journal of ophthalmology. 2010;150(3):315-24.e1.

Aiello LP. Angiogenic pathways in diabetic retinopathy. The New England journal of medicine. 2005;353(8):839-41.

Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. The New England journal of medicine. 1994;331(22):1480-7.

Albert D.M, Jakobiec F. A. Principles and Practice of Ophthalmology. Philadelphia,PA: W.B. Saunders Company; 2000.

Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy. Semin Ophthalmol. 1999;14(4):223-32.

Bandello F, Cunha-Vaz J, Chong NV, Lang GE, Massin P, Mitchell P, et al. New approaches for the treatment of diabetic macular oedema: recommendations by an expert panel. Eye (London, England). 2012;26(4):485-93.

Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. Survey of ophthalmology. 2009;54(1):1-32.

Bressler NM, Bressler SB, Gragoudas ES. Clinical characteristics of choroidal neovascular membranes. Archives of ophthalmology (Chicago, Ill : 1960). 1987;105(2):209-13.

Bringmann A, Reichenbach A, Wiedemann P. Pathomechanisms of cystoid macular edema. Ophthalmic research. 2004;36(5):241-9.

Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet (London, England). 2010;376(9735):124-36.

Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. Diabetes care. 2003;26(9):2653-64.

Cruess A, Zlateva G, Xu X, Rochon S. Burden of illness of neovascular age-related macular degeneration in Canada. Can J Ophthalmol. 2007;42(6):836-43.

De Jong PT, Bergen AA, Klaver CC, Van Duijn CM, Assink JM. Age-related maculopathy: its genetic basis. Eye (London, England). 2001;15(Pt 3):396-400.

ETDRS Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Archives of ophthalmology (Chicago, Ill : 1960). 1985;103(12):1796-806.

EYLEA HD (aflibercept) [USPI]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2023.

Ferrara N. VEGF: an update on biological and therapeutic aspects. Current opinion in biotechnology. 2000;11(6):617-24.

Flores R, Carneiro Â, Vieira M, Tenreiro S, Seabra MC. Age-Related Macular Degeneration: Pathophysiology, Management, and Future Perspectives. Ophthalmologica Journal international d'ophtalmologie International journal of ophthalmology Zeitschrift fur Augenheilkunde. 2021;244(6):495-511.

Gündüz K, Bakri SJ. Management of proliferative diabetic retinopathy. Compr Ophthalmol Update. 2007;8(5):245-56.

Hadziahmetovic M, Malek G. Age-Related Macular Degeneration Revisited: From Pathology and Cellular Stress to Potential Therapies. Frontiers in cell and developmental biology. 2020;8:612812.

ICH. ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 1994.

Jaffe GJ, Kaiser PK, Thompson D, Gibson A, Saroj N, Vitti R, et al. Differential Response to Anti-VEGF Regimens in Age-Related Macular Degeneration Patients with Early Persistent Retinal Fluid. Ophthalmology. 2016;123(9):1856-64.

Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. The New England journal of medicine. 2008;358(24):2606-17.

Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Archives of ophthalmology (Chicago, Ill : 1960). 1984;102(4):527-32.

Miller JW. Age-related macular degeneration revisited--piecing the puzzle: the LXIX Edward Jackson memorial lecture. American journal of ophthalmology. 2013;155(1):1-35.e13.

Mittra RA, Ramsay RC. New treatments for age-related macular degeneration. Minn Med. 2009;92(6):41-4.

Moss SE, Klein R, Klein BE. The 14-year incidence of visual loss in a diabetic population. Ophthalmology. 1998;105(6):998-1003.

Moss SE, Klein R, Klein BE. Ten-year incidence of visual loss in a diabetic population. Ophthalmology. 1994;101(6):1061-70.

Nguyen QD, Tatlipinar S, Shah SM, Haller JA, Quinlan E, Sung J, et al. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. American journal of ophthalmology. 2006;142(6):961-9.

Pendergast SD. Vitrectomy for diabetic macular edema associated with a taut premacular posterior hyaloid. Current opinion in ophthalmology. 1998;9(3):71-5.

Praidou A, Klangas I, Papakonstantinou E, Androudi S, Georgiadis N, Karakiulakis G, et al. Vitreous and serum levels of platelet-derived growth factor and their correlation in patients with proliferative diabetic retinopathy. Curr Eye Res. 2009;34(2):152-61.

Schmidt-Erfurth UM, Richard G, Augustin A, Aylward WG, Bandello F, Corcòstegui B, et al. Guidance for the treatment of neovascular age-related macular degeneration. Acta Ophthalmol Scand. 2007;85(5):486-94.

Sivaprasad S, Gupta B, Crosby-Nwaobi R, Evans J. Prevalence of diabetic retinopathy in various ethnic groups: a worldwide perspective. Survey of ophthalmology. 2012;57(4):347-70.

Soubrane G, Cruess A, Lotery A, Pauleikhoff D, Monès J, Xu X, et al. Burden and health care resource utilization in neovascular age-related macular degeneration: findings of a multicountry study. Archives of ophthalmology (Chicago, Ill : 1960). 2007;125(9):1249-54.

Tan CS, Ngo WK, Chay IW, Ting DS, Sadda SR. Neovascular Age-Related Macular Degeneration (nAMD): A Review of Emerging Treatment Options. Clinical ophthalmology (Auckland, NZ). 2022;16:917-33.

Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology. 2016;123(6):1351-9.

Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. The Lancet Global health. 2014;2(2):e106-16.

Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes care. 2012;35(3):556-64.

19. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 3b Single-Arm Study of Aflibercept 8 mg in Participants With Neovascular Age-Related Macular Degeneration (nAMD) or Diabetic Macular Edema (DME) 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 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 Phase 3b Single-Arm Study of Aflibercept 8 mg in Participants With Neovascular Age-Related Macular Degeneration (nAMD) or Diabetic Macular Edema (DME)

Protocol Number: Protocol VGFTe-HD-OD-2444

Protocol Version: Amendment 3

See appended electronic signature page

Sponsor's Responsible Medical 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

APPENDIX 1. [redacted]

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Signature Page for VV-RIM-00400839 v1.0

Approval/eSignature	[redacted] 25-Mar-2025 17:16:22 GMT+0000

Approval/eSignature	[redacted] 25-Mar-2025 17:19:07 GMT+0000

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