Document Type:	Clinical Study Protocol
Official Title:	Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Aflibercept 8 mg in Macular Edema Secondary to Retinal Vein Occlusion
NCT Number:	NCT05850520
Document Date:	07 FEB 2023

Title Page

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Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Aflibercept 8 mg in Macular Edema Secondary to Retinal Vein Occlusion

Protocol Number: 22153

Protocol Version: Final, 1.0

Compound Number: BAY 86-5321/aflibercept

Short Title: Efficacy and Safety of High Dose Aflibercept in Macular Edema Secondary to Retinal Vein Occlusion

Study Phase: 3

Acronym: QUASAR

Sponsor Name: Bayer AG

Legal Registered Address:

Bayer AG, 51368 Leverkusen, Germany

Regulatory Agency Identifier Number(s):

Investigational New Drug (IND): 12462 (Regeneron Pharmaceuticals, Inc.)

EU-CT number: 2022-502174-16-00

Protocol Date: 07 FEB 2023

PPD Role: PPD

This is an electronically generated document that does not bear any Sponsor signatures. The signature of the Sponsor's medically responsible person is filed in the trial master file (TMF) and available on request.

Medical Monitor name and contact information will be provided separately.

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List of Abbreviations

Abbreviation	Description
ADE	adverse device effect
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
APAC	Asia-Pacific
APTC	anti-platelet trialists' collaboration
ATE	arterial thromboembolic events
AxMP	auxiliary medicinal product
BCVA	best-corrected visual acuity
BMI	body mass index
BRVO	branch retinal vein occlusion
CE	conformité européenne
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRVO	central retinal vein occlusion
CST	central subfield thickness
DL-AAA	DL-α-aminoadipic acid
DMC	data monitoring committee
DME	diabetic macular edema
DRM	dose regimen modification
eCRF	electronic case report form
ECG	electrocardiogram
EoS	end of study
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
FAS	Full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FP	fundus photography
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
HRVO	hemiretinal vein occlusion
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	intraocular pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IVT	Intravitreal(ly)
MDR	Medical Device Regulation

Abbreviation	Description
MMRM	mixed model for repeated measurements
nAMD	neovascular age-related macular degeneration
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
NI	non-inferiority
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
PCR	polymerase chain reaction
PCSV	potentially clinically significant value
PlGF	placental growth factor
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PT	preferred term
QoL	quality of life
Q4W	every 4 weeks
Q8W	every 8 weeks
RVO	retinal vein occlusion
SADE	serious adverse device effects
SAE	serious adverse event
SAF	Safety analysis set
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD-OCT	spectral domain optical coherence tomography
SDLL	Source Data Location List
SoA	schedule of activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
T&E	treat and extend
TEAE	treatment-emergent adverse event
TMF	trial master file
US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WOCBP	woman (women) of childbearing potential
YAG	yttrium-aluminum-garnet

1. Protocol Summary

1.1 Synopsis

Protocol Title: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Aflibercept 8 mg in Macular Edema Secondary to Retinal Vein Occlusion

Short Title: Efficacy and Safety of High Dose Aflibercept in Macular Edema Secondary to Retinal Vein Occlusion

Regulatory Agency Identifier Number(s): EU-CT number: 2022-502174-16-00

Envisaged Indication: Macular edema secondary to retinal vein occlusion

Rationale:

Retinal vein occlusion (RVO) is one of the most frequent causes of visual loss from diseases affecting the retinal vessels of the eye. The 2 major RVO categories are central RVO

(CRVO), with blockage of the single, central vein draining blood from the retina, and branch RVO (BRVO), where one or more of the branches of the central retinal vein are occluded. A less frequent subtype is hemiretinal vein occlusion (HRVO), where branches from the superior or inferior hemisphere are occluded, sharing characteristics with both CRVO and BRVO. All subtypes result in impaired venous drainage from the eye, which may lead to increased venous pressure, reduced arterial perfusion, and retinal ischemia. One result of retinal non-perfusion is an increase in the production of vascular endothelial growth factor (VEGF). The VEGF levels in aqueous humor from eyes with RVO can be more than 100 times higher than normal. Increased expression of VEGF can lead to vascular permeability, macular edema, retinal hemorrhage, and neovascularization. Patients with central macular edema secondary to RVO lose visual acuity, and the visual prognosis, if untreated, is often poor.

Vascular endothelial growth factor mediates endothelial cell hypertrophy which leads to a reduction of capillary luminal diameter. This, in turn, results in an increase of intravascular pressure over the length of a retinal vessel. The resulting decrease in the blood flow in the retinal capillary augments ischemia and hypoxia, thereby increasing the expression of VEGF which maintains this pathogenic cycle.

Because of the role it plays in the pathology of macular edema secondary to RVO, VEGF has become an important drug target in treatment strategies. The use of intravitreal (IVT) anti-VEGF agents, including aflibercept 2 mg, for the treatment of macular edema secondary to RVO has become the standard of care. The recommended dose for aflibercept 2 mg in the United States Prescribing Information (USPI) is once every 4 weeks (Q4W).

Aflibercept has a high binding affinity for VEGF and placental growth factor (PlGF). It neutralizes vascular endothelial growth factor receptor 1/2 (VEGFR1/R2)-mediated biological activity leading to improvement of macular edema secondary to RVO.

Increasing the total amount of anti-VEGF therapeutic protein administered with a higher concentration formulation compared with currently available agents is a potential way to bring further benefits to patients with chorioretinal vascular diseases including neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME) and RVO. Delivering a larger amount of drug through a higher concentration formulation has the potential to increase the drug's biological duration of action and provide greater efficacy particularly in anatomic measures. This creates the potential not only for greater efficacy, but for reducing patient burden by extending the interval between IVT injections and consequently the overall number of doses. This reduction in treatment burden is particularly important in this population where many patients are still working.

Based on this rationale, the current study aims to test a novel IVT formulation with a higher concentration of aflibercept. The development candidate, aflibercept 8 mg (provided at a concentration of 114.3 mg/mL), targets IVT delivery of increased molar concentrations of VEGF inhibitors relative to the formulation currently approved for Eylea® 2 mg. The efficacy and safety of aflibercept 8 mg has recently been demonstrated in the ongoing Phase 2/3 PHOTON study in patients with DME and the ongoing Phase 3 PULSAR study in patients with nAMD. In DME, 91% and 89% of patients were able to be maintained on a 12- or 16-week regimen, respectively, with the 8 mg formulation while achieving best-corrected visual acuity (BCVA) results non-inferior to those achieved with the 2 mg formulation. In nAMD, 79% and 77% of patients were able to be maintained on a 12- or 16-week regimen, respectively, with the 8 mg formulation while achieving BCVA results non-inferior to those achieved with the 2 mg formulation. The safety profile of aflibercept 8 mg in Phase 3

PULSAR study and Phase 2/3 PHOTON study were consistent with the known safety profile of aflibercept 2 mg and no dose relationship and no new safety signal was observed in the two studies.

The current study will investigate the efficacy and safety of aflibercept 8 mg with the intent of achieving non-inferior BCVA, while extending the dosing interval to reduce the number of injections and potentially improving visual and/or anatomic outcomes for aflibercept 8 mg vs. the currently approved aflibercept 2 mg dose regimen as well as maintaining the same safety profile as aflibercept 2 mg.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To determine if treatment with aflibercept 8 mg Q8W provides non-inferior BCVA change compared to aflibercept 2 mg Q4W	**Primary Endpoint:** • Change from baseline in BCVA measured by the ETDRS letter score at Week 36
Secondary - Efficacy	
• To determine if treatment with aflibercept 8 mg Q8W requires less injections compared to aflibercept 2 mg Q4W	**Key Secondary Endpoint** • Number of active injections from baseline to Week 64[1] **Secondary Endpoint** • Number of active injections from baseline to Week 36
• To determine the effect of aflibercept 8 mg Q8W compared to aflibercept 2 mg Q4W on other visual and anatomic measures of response	**Secondary Endpoints:** • Change from baseline in BCVA measured by the ETDRS letter score at Week 44[2] • Change from baseline in BCVA measured by the ETDRS letter score at Week 64 • Participant gaining at least 15 letters in BCVA from baseline at Weeks 36 and 64 • Participant achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Weeks 36 and 64 • Participant having no IRF and no SRF in the center subfield at Weeks 36 and 64 • Change from baseline in CST at Weeks 36 and 64
• To assess the efficacy of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W on vision-related QoL	• Change from baseline in NEI-VFQ-25 total score at Weeks 36 and 64
Secondary - Safety	
• To evaluate the safety of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W	• Occurrence of TEAEs and SAEs through Weeks 36 and 64
Secondary - Other	
• To evaluate duration of effect of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W	• Participant dosed only Q8W through Week 36 in the 8 mg Q8W group • Participant having last treatment interval ≥12 or of 16 weeks at Week 64 • Participant having next intended interval ≥12, ≥16 or of 20 weeks at Week 64
• To evaluate the PK of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W	• Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Weeks 36 and 64

Objectives	Endpoints
Exploratory	
• To determine the effect of aflibercept 8 mg Q8W compared to aflibercept 2 mg Q4W on further visual and anatomic measures of response	• Change from baseline in BCVA measured by the ETDRS letter score at each visit • Participant with vision changes of at least 5, 10, or 15 letters in BCVA from baseline at each visit • Participant with no IRF and no SRF in the center subfield at each visit • Time to fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield) • Participant having sustained fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield) • Change in area of retinal ischemia at Weeks 36 and 64 • Change in the area of fluorescein leakage at Weeks 36 and 64
• To study molecular drivers of RVO or related diseases, clinical efficacy of aflibercept, and affected molecular pathways	• Evaluation of clinical efficacy parameters by repertoire or frequency of genetic alterations (genomics substudy) • Treatment related changes in circulating biomarkers (FBR)

AE=adverse event, BCVA=best-corrected visual acuity, CST=central subfield thickness, ETDRS=Early Treatment Diabetic Retinopathy Study, FBR=future biomedical research, IRF=intraretinal fluid, NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, PK=pharmacokinetics, QoL=quality of life, Q4W=every 4 weeks, Q8W=every 8 weeks, RVO=retinal vein occlusion, SAE=serious adverse event, SRF=sub-retinal fluid, TEAE=treatment-emergent adverse event

[1] Where premature treatment discontinue due to treatment related AE is considered as treatment-failure and the number of active injections from baseline to Week 64 is set to an unfavorable outcome (equal to 16, the maximum value).

[2] For the 8 mg/5 and 2 mg groups only.

The primary estimand for the primary objective is described by the following attributes:

- Population: Adult participants with treatment-naïve macular edema secondary to RVO
- Endpoint: Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 36
- Treatment condition:
  - Aflibercept 8 mg administered with 3 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
  - Aflibercept 8 mg administered with 5 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
  - Aflibercept 2 mg administered Q4W until Week 32, followed by adjustment of treatment intervals according to treatment response

  A delayed active injection resulting in an injection interval up to 4 weeks longer than planned is considered to be in line with the treatment regimen of interest.
- Intercurrent events and strategies:
  - Premature treatment discontinuation – addressed by the hypothetical strategy (had participants continued treatment until Week 36)

  - Use of prohibited medication – addressed by the hypothetical strategy (had prohibited medications not been taken)
  - Missed study intervention:
    - Missed active injection resulting in an injection interval up to 4 weeks longer than planned: treatment policy strategy (the effect of a missed active injection will be included in the estimate of the treatment effect)
    - Missed active injection resulting in an injection interval more than 4 weeks longer than planned: hypothetical strategy (had injection not been missed or delayed by less than 4 weeks)
- Population-level summary: Difference in mean change from baseline to Week 36 in BCVA between each aflibercept 8 mg group and the aflibercept 2 mg group

The secondary estimand for the secondary objective is described by the following attributes:

- Population: Adult participants with treatment-naïve macular edema secondary to RVO
- Endpoint: Number of active injections from baseline to Week 64 where premature treatment discontinuations due to treatment related adverse event (AE) is considered as treatment-failure and the number of injections is set to an unfavorable outcome (equal to 16, the maximum value)
- Treatment condition:
  - Aflibercept 8 mg administered with 3 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
  - Aflibercept 8 mg administered with 5 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
  - Aflibercept 2 mg administered Q4W until Week 32, followed by adjustment of treatment intervals according to treatment response

  The minimum treatment interval is 4 weeks while the study duration allows the maximum treatment interval to be 16 weeks. Imperfect adherence other than premature treatment discontinuation is considered as part of the treatment.
- Intercurrent events and strategies:
  - Premature treatment discontinuation
    - Due to lack-of-efficacy: Hypothetical strategy (had participants continued treatment until Week 64)
    - Due to treatment related AEs: Composite strategy (addressed in the endpoint definition)
    - Due to treatment unrelated AEs and other reasons: Hypothetical strategy (had participants continued treatment until Week 64)
  - Missed study intervention – addressed by treatment policy strategy (the effect of a missed active injection will be included in the estimate of the treatment effect)
- Population-level summary: Difference in mean number of active injections up to Week 64 between each aflibercept 8 mg group and the aflibercept 2 mg group

Overall Design Synopsis:

This is a Phase-3, multi-center, randomized, double-masked, active-controlled clinical study to assess the efficacy and safety of high dose (8 mg) aflibercept administered IVT compared to 2 mg aflibercept treatment in participants with treatment-naïve macular edema secondary to RVO.

The study population consists of men and women 18 years and older who have been diagnosed with macular edema secondary to RVO (BRVO, CRVO, or HRVO), involving the center of the macula, with a BCVA letter score of 73 to 24 (20/40 to 20/320) in the study eye.

Only 1 eye per participant will be enrolled in the study. If a participant's fellow (non-study) eye requires anti-VEGF treatment (for any approved indication in the respective country) during the participant's involvement in the study, the fellow eye should be treated with aflibercept 2 mg according to the approved treatment regimen in the respective country, irrespective of the randomization assignment of the participant. In countries where aflibercept 2 mg is not approved for treatment of RVO, the fellow eye may be treated with aflibercept 2 mg upon approval by an appropriate regulatory body and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) in the respective country. Otherwise, another locally approved treatment option should be used. The aflibercept 2 mg used for treatment of the fellow eye will wherever possible be provided by the Sponsor in compliance with local regulations. In cases where this supply is not possible, the costs of aflibercept 2 mg will be supported by the Sponsor in compliance with local regulations.

A total of approximately 822 eligible participants with macular edema secondary to RVO are planned to be randomized in a 1:1:1 ratio to aflibercept 8 mg every 8 weeks (Q8W) after 3 initial Q4W initiation doses group (8 mg/3) or aflibercept 8 mg Q8W after 5 initial Q4W initiation doses group (8 mg/5) or aflibercept 2 mg Q4W group (2 mg). A minimum of 40% of the eligible participants for each stratum CRVO or HRVO, and BRVO are planned to be included in this study. The randomization will be stratified by RVO type ([CRVO or HRVO] vs. BRVO), geographic region (Japan vs. Rest of Asia-Pacific [APAC] vs. America vs. Europe), and baseline BCVA (<60 vs. ≥60 letters). For the purpose of stratification by RVO type, HRVO participants will be included in the CRVO stratum.

The study consists of a screening/baseline period, a treatment period with duration of 60 weeks, and an end of study (EoS) visit at Week 64. No study intervention will be administered at the EoS visit at Week 64.

Figure 1-1 shows the dosing schedule. Study visits will be scheduled Q4W throughout the study duration. At every visit until Week 60, the participants will receive an active or sham injection for masking purposes. During the first 32 weeks, the 2 mg group will receive an active injection at every visit while the 8 mg groups will initiate treatment with injections Q4W for a total of 3 doses or will initiate treatment with injections Q4W for a total of 5 doses, followed by extension of the treatment interval of 8 weeks. Beginning at Week 36 through Week 60, treat and extend (T&E) will be employed for the 2 mg group and 8 mg/3 group and beginning at Week 44 through Week 60 for the 8 mg/5 group. Extension or shortening of the dosing interval will depend on meeting dose regimen modification (DRM) criteria. The DRM criteria may also indicate active injections for the 8 mg groups at Weeks 20 (8 mg/3) and 28 (8 mg/3 and 8 mg/5) for participants in the need of treatment.

Figure 1-1: Dosing Schedule

Year 1	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36 PE	Wk 40	Wk 44 SE[1]	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64 KSE
AFL 2 mg	X	X	X	X	X	X	X	X	X	T&E →							
AFL 8 mg/3	X	X	X	O	X	O[2]	X	O[2]	X	T&E →							
AFL 8 mg/5	X	X	X	X	X	O	X	O[2]	X	O[2]	X	T&E →					

DRM Criteria

Shortening Criteria:
- BCVA loss >5 letters from reference visit, AND
- >50 µm increase in CST from reference visit

Interval shortening possible from W16 for 8 mg/3, W24 for 8 mg/5, and W40 for 2mg
Reference is W12 for 8 mg/3, W20 for 8 mg/5 and 2 mg

Extension Criteria:
- BCVA loss <5 letters from reference visit, AND
- CST thickness <320 µm including Bruch's membrane / <300 µm excluding Bruch's membrane

Interval extension possible from W32 for 8 mg/3, W40 for 8 mg/5 and W32 for 2 mg
Reference is W12 for 8 mg/3, W20 for 8 mg/5 and 2 mg

AFL=aflibercept, BCVA=best-corrected visual acuity, CST=central subfield thickness, DRM=dose regimen modification, KSE=key secondary endpoint, O=sham injection visit, PE=primary endpoint, SE=secondary endpoint, SD-OCT=spectral domain optical coherence tomography, T&E=treat and extend, Wk=week, X=active injection visit, -=no injection, 8 mg/3=8 mg Q8W after 3 initial Q4W doses, 8 mg/5=8 mg Q8W after 5 initial Q4W doses.
[1]=Secondary endpoint BCVA change from baseline to Week 44 for 2 mg and 8 mg/5 groups.
[2]=Participants meeting interval shortening criteria at any dosing visit starting from Week 16 for 8 mg/3, Week 24 for 8 mg/5 or Week 40 for 2 mg have their dosing interval shortened by 4 weeks. Interval extension is possible from Week 32 for 8 mg/3, from Week 40 for 8 mg/5, and from Week 32 for 2 mg depending on DRM.

DRM Shortening Criteria:

Beginning at Week 16 for the 8 mg/3 group, Week 24 for the 8 mg/5 group and Week 40 for the 2 mg group, participants will be eligible to have their dosing interval shortened by 4 weeks if both the following DRM shortening criteria are met **at a dosing visit**:

1. Best-corrected visual acuity loss >5 letters from reference visit*, AND
2. >50 µm increase in central subfield thickness (CST) from reference visit*

   *Reference visits are Week 12 for the 8 mg/3 group, Week 20 for the 8 mg/5 group and Week 20 for the 2 mg group.

For example, in case the DRM shortening criteria are met at Week 16, participants will have their following dosing intervals shortened to 4 weeks, thus, will receive additional active doses at Weeks 20 and 28 and remain on 4-week intervals until end of study or DRM criteria for interval extension are met. In case the DRM shortening criteria are met at Week 24, participants will receive an additional active dose at Week 28 and remain on 4 week intervals until end of study or DRM criteria for interval extension are met. The minimum planned interval between dosing visits is 4 weeks. The actual interval between injections may be shorter than 28 days due to the allowed visit windows. Once a participant has their treatment interval shortened to Q4W, they will continue to be treated Q4W until end of study or DRM criteria for extension are met, as described below.

DRM Extension Criteria Starting at Weeks 32 and 40:

Starting at Week 32 for the 2 mg and 8 mg/3 groups, and starting at Week 40 for the 8 mg/5 group, participants will be eligible for interval extension (by 4-week increments) if both the following DRM extension criteria are met **at a dosing visit**:

1. Best-corrected visual acuity loss <5 letters from reference visit*, AND

2. CST thickness <320 µm if including Bruch's membrane (e.g., Heidelberg Spectralis), or <300 µm if excluding Bruch's membrane (e.g., Cirrus or Topcon) on optical coherence tomography (OCT)

   *Reference visits are Week 12 for the 8 mg/3 group, Week 20 for the 8 mg/5 group and Week 20 for the 2 mg group.

When these criteria are met at a dosing visit, the participant receives the planned dose at that visit and has the next treatment interval extended by 4 weeks (e.g., if the last interval was 4 weeks, the next will be 8 weeks). If at a later dosing visit, the DRM extension criteria are met again, the participant receives the planned dose at that visit and the next interval will be extended by another 4 weeks (e.g., if the last interval was 8 weeks, the next will be 12 weeks).

For the assessment of DRM shortening and extension criteria, in case measurement is not available at the reference visit, the most recent measurement from previous visit should be used instead. For example, if reference visit is Week 12 and this measurement is not available, the Week 8 measurement should be used instead. If both Weeks 12 and 8 measurements are not available, the Week 4 measurement should be used instead. In case there are no measurements at Weeks 4, 8, and 12, the participant will be considered non-compliant and discontinued from the study.

For participants who do not meet the criteria for shortening or extension of the interval, the current dosing interval will be maintained.

All assessments of DRM criteria will be performed by Investigator evaluations of BCVA and OCT examinations. The same model of OCT machine must be used for individual participants throughout the study to provide comparable measurements.

Short Summary:

The purpose of this study is to investigate the efficacy and safety of aflibercept 8 mg in participants with macular edema secondary to RVO.

Total study duration will be up to 67 weeks (include screening phase [3 weeks] and EoS [Week 64]).

Study details include:

- Study duration per participant:
  - Screening phase: Up to 3 weeks
  - Treatment phase: Up to 60 weeks
  - End of study: Week 64
- Visit frequencies: Screening visit, Weeks 0 (baseline), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, and 64. Following discontinuation of study intervention, participants will be followed unless they withdraw their informed consent for study participation or are lost to follow-up.

Number of Participants:

Approximately 822 participants will be randomized in 1:1:1 ratio. The randomization will be stratified by RVO type ([CRVO or HRVO] vs. BRVO), geographic region (Japan vs. Rest of APAC vs. America vs. Europe), and baseline BCVA (<60 vs. ≥60 letters). A minimum of 40% of the participants per RVO type ([CRVO or HRVO] vs. BRVO) are targeted to be randomized. Approximately 10% of the study participants are planned to be recruited in Japan, to allow appropriate representation in the overall study population and each subgroup.

Study Groups and Duration:

- Aflibercept 8 mg/3:

  Aflibercept 8 mg administered with 3 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and adjustment of intervals according to treatment response. The 8 mg group will receive an active or sham injection every visit for masking purpose.
- Aflibercept 8 mg/5:

  Aflibercept 8 mg administered with 5 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks until Week 36 and adjustment of intervals according to treatment response. The 8 mg group will receive an active or sham injection every visit for masking purpose.
- Aflibercept 2 mg:

  Aflibercept 2 mg administered Q4W until Week 32 followed by adjustment of intervals according to treatment response. The 2 mg group will receive an active or sham injection every visit for masking purposes.

Data Monitoring Committee: Yes

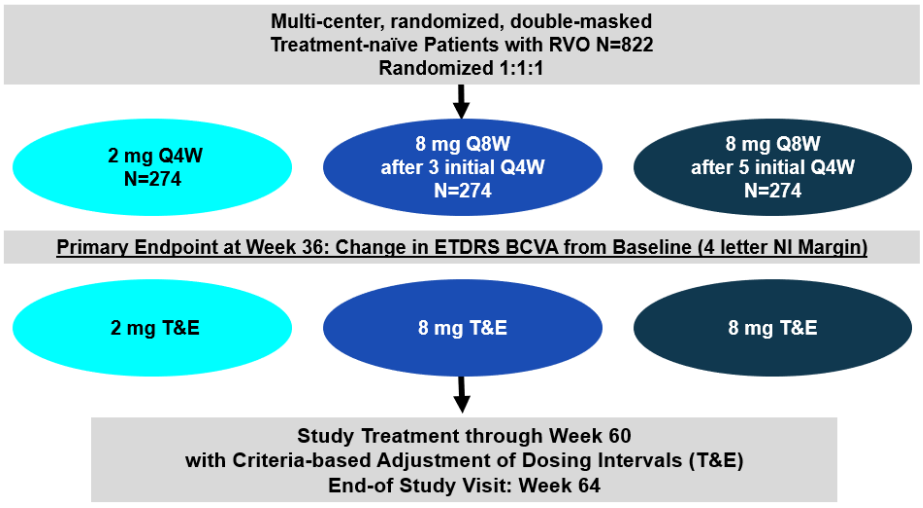
An independent data monitoring committee (DMC) (board) has been appointed for this study. The independent DMC is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

Anti-Platelet Trialists' Collaboration Adjudication Committee: Yes

Potential arterial thromboembolic events (ATEs) will be evaluated by a masked adjudication committee according to criteria formerly applied and published by the anti-platelet trialists' collaboration (APTC) prior to database unmasking.

1.2 Schema

Figure 1-2: Study Design



BCVA=Best-corrected Visual Acuity, ETDRS=Early Treatment of Diabetic Retinopathy Study, NI=non-inferiority, Q4W=every 4 weeks, Q8W=every 8 weeks, RVO=retinal vein occlusion, T&E=treat and extend

1.3 Schedule of Activities

Table 1–1: Schedule of Activities

Study Phase	Screening	Baseline	Treatment															EoS or ED
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Week	**-3**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**
Day	**-21 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**
Window (day)[a]			**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Administrative:																		
ICF	X																	
Genomic Substudy ICF[b]	X																	
FBR ICF[c]	X																	
Inclusion/Exclusion Eligibility	X	X[d]																
Medical History	X																	
Demographics	X																	
Prior and/or Concomitant Medications/ Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X																
Study Intervention[e]:																		
Study Intervention (Active or Sham)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
DRM Assessment[f]						X	X	X	X	X	X	X	X	X	X	X	X	
Ocular Efficacy and Safety (bilateral unless indicated):																		
NEI-VFQ-25[g]		X									X							X
BCVA (ETDRS) and Refraction	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit Lamp Examination[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect Ophthalmoscopy[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FA, FP[k]	X				X						X							X
SD-OCT[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT-A[l]	X				X				X		X				X			X

Study Phase	Screening	Baseline	Treatment															EoS or ED
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Week	**-3**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**
Day	**-21 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**
Window (day)[a]			**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Nonocular Safety:																		
Physical Examination	X										X							X
Vital Signs[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X										X							X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[n]:																		
Hematology	X										X							X
Blood Chemistry	X										X							X
Pregnancy Test (WOCBP)[o]	X Serum	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine
Urinalysis, UPCR	X										X							X
Pharmacokinetics and Other Sampling:																		
PK Sample (Sparse)[p]		X	X		X	X[p]		X			X							X
Genomic DNA Sample (optional)[b]		X																

AE=adverse event, BCVA=best corrected visual acuity, DNA=deoxyribonucleic acid, DRM=dose regimen modification, ECG=electrocardiogram, ED=early discontinuation, EoS=end of study, ETDRS=Early Treatment Diabetic Retinopathy Study, FA=fluorescein angiography, FBR=future biomedical research, FP=fundus photography, ICF=informed consent form, IOP=intraocular pressure, IVT=intravitreal(ly), NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, OCT-A=optical coherence tomography angiography, PK=pharmacokinetics, SD-OCT=spectral domain optical coherence tomography, UPCR=urine protein:creatinine ratio, WOCBP=women of childbearing potential

Footnotes for the Schedule of Activities (SoA) Table

a. Visit schedules may deviate by up to ±5 days. Set schedule visits use baseline for the calculation. The procedures required at each visit have to be complete within 3 days, i.e., split visits are allowed. Additionally, all procedures have to be complete within the 5-day window. Slit lamp (anterior segment), IOP measurement, and indirect ophthalmoscopy are recommended to take place on the same day as the IVT injection.

b. The optional genomic substudy ICF should be presented to participants at the screening visit and may be signed at any subsequent visit at which the participant chooses to participate after screening. The genomic DNA blood sample should be collected on Day 1/baseline (pre-injection) or at any time during the study, only from participants who consent to participate in the genomic substudy. Substudy is not applicable for China.

c. The optional FBR ICF should be presented to participants and signed at the screening visit. No additional blood sample is required – remaining blood samples (from e.g., PK) may be used. Substudy is not applicable for China.

d. Inclusion/exclusion criteria will be evaluated at screening and baseline to confirm participant's eligibility. The Investigator is responsible for confirming that any changes between screening and baseline do not affect the participant's eligibility.

e. Following study intervention injection or sham procedure, participants will be observed for at least 30 minutes.

f. For masking purposes, assessments for DRM will be performed in all participants at all visits starting from Week 16. Actual DRMs will be implemented based on outcome at active treatment visits.

g. National Eye Institute Visual Functioning Questionnaire-25 to be administered in a quiet room by a masked study-related person trained to administer this type of questionnaire, preferably before other visit procedures are performed.

h. Intraocular pressure will be measured at all study visits (bilateral). On days when study intervention is administered, IOP should be measured approximately 30 to 60 minutes (±10 minutes so measure should be at least 20 minutes after IVT injection and no more than 70 minutes after IVT injection) after administration of study intervention (study eye only) by the unmasked Investigator (or designee). The exact timing is left to the discretion of the unmasked Investigator. Intraocular pressure will be measured using Goldman applanation tonometry, rebound tonometry Icare, or Tonopen and the same method of measurement must be used in each participant throughout the study.

i. Slit lamp examination will be performed bilaterally.

j. Indirect ophthalmoscopy will be performed bilaterally at all visits. On days when study intervention is administered, it should also be performed immediately after administration of study intervention (study eye only).

k. The same SD-OCT/FA/FP imaging system used at screening and Day 1 must be used at all follow-up visits in each participant. Images will be taken in both eyes before dosing (active or sham injection).

l. Optical coherence tomography angiography is optional at all sites that have the relevant equipment. If OCT-A cannot be performed at the screening visit, it may be done at baseline visit.

m. Vital signs (body temperature, blood pressure, and heart rate) should be measured per the procedure outlined in the study manual. Vital signs should be measured prior to injection and any blood sampling. Timing of all blood pressure assessments should be within 2 hours of clock time of dosing on Day 1.

n. All samples collected for laboratory assessments should be obtained prior to administration of fluorescein, and prior to administration of study intervention.

o. For WOCBP, a negative serum pregnancy test at screening is required for eligibility. A negative urine pregnancy test is required before any treatment is administered at subsequent visits.

p. Sparse PK sampling will be performed in all participants. Any PK sampling will be done prior to dosing if scheduled at the sampling time point. An additional sample to be taken in 1 to 10 days after fifth injection (Please note: The cross is set at Day 113, but the cross refers only to the one sample 1 to 10 days after injection at Day 113).

2. Introduction

2.1 Study Rationale

Retinal vein occlusion (RVO) is one of the most frequent causes of visual loss from diseases affecting the retinal vessels of the eye (Rogers et al. 2010). The 2 major RVO categories are central RVO (CRVO), with blockage of the single, central vein draining blood from the retina, and branch RVO (BRVO), where one or more of the branches of the central retinal vein are occluded. A less frequent subtype is hemiretinal vein occlusion (HRVO), where branches from the superior or inferior hemisphere are occluded, sharing characteristics with both CRVO and BRVO. All subtypes result in impaired venous drainage from the eye, which may lead to increased venous pressure, reduced arterial perfusion, and retinal ischemia (Brown et al. 2012, Korobelnik et al. 2014, and Ogura et al. 2014). One result of retinal non-perfusion is an increase in the production of vascular endothelial growth factor (VEGF) (Aiello et al. 1994). The VEGF levels in aqueous humor from eyes with RVO can be more than 100 times higher than normal (Noma et al. 2011). Increased expression of VEGF can lead to vascular permeability, macular edema, retinal hemorrhage, and neovascularization (Brown et al. 2012, Korobelnik et al. 2014, Ogura et al. 2014). Patients with central macular edema secondary to RVO lose visual acuity, and the visual prognosis, if untreated, is often poor (Holz et al. 2013).

Vascular endothelial growth factor mediates endothelial cell hypertrophy which leads to a reduction of capillary luminal diameter. This, in turn, results in an increase of intravascular pressure over the length of a retinal vessel. The resulting decrease in the blood flow in the retinal capillary augments ischemia and hypoxia, thereby increasing the expression of VEGF which maintains this pathogenic cycle (Aiello et al. 1994).

Because of the role, it plays in the pathology of macular edema secondary to RVO, VEGF has become an important drug target in treatment strategies (Ogura et al. 2014, Heier et al. 2014). The use of intravitreal (IVT) anti-VEGF agents, including aflibercept 2 mg, for the treatment of macular edema secondary to RVO has become the standard of care. The recommended dose for aflibercept 2 mg in the United States Prescribing Information (USPI) is once every 4 weeks (Q4W).

Aflibercept has a high binding affinity for VEGF and placental growth factor (PlGF). It neutralizes vascular endothelial growth factor receptor 1/2 (VEGFR1/R2)-mediated biological activity leading to improvement of macular edema secondary to RVO.

Increasing the total amount of anti-VEGF therapeutic protein administered with a higher concentration formulation compared with currently available agents is a potential way to bring further benefits to patients with chorioretinal vascular diseases including neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME) and RVO. Delivering a larger amount of drug through a higher concentration formulation has the potential to increase the drug's biological duration of action and provide greater efficacy particularly in anatomic measures. This creates the potential not only for greater efficacy, but for reducing patient burden by extending the interval between IVT injections and consequently the overall number of doses. This reduction in treatment burden is particularly important in this population where many patients are still working.

Based on this rationale, the current study aims to test a novel IVT formulation with a higher concentration of aflibercept. The development candidate, aflibercept 8 mg (provided at a concentration of 114.3 mg/mL), targets IVT delivery of increased molar concentrations of

VEGF inhibitors relative to the formulation currently approved for Eylea® 2 mg. The efficacy and safety of aflibercept 8 mg has recently been demonstrated in the ongoing Phase 2/3 PHOTON study in patients with DME and the ongoing Phase 3 PULSAR study in patients with nAMD. In DME, 91% and 89% of patients were able to be maintained on a 12- or 16-week regimen, respectively, with the 8 mg formulation while achieving best-corrected visual acuity (BCVA) results non-inferior to those achieved with the 2 mg formulation. In nAMD, 79% and 77% of patients were able to be maintained on a 12- or 16-week regimen, respectively, with the 8 mg formulation while achieving BCVA results non-inferior to those achieved with the 2 mg formulation. The safety profile of aflibercept 8 mg in Phase 3 PULSAR study and Phase 2/3 PHOTON study were consistent with the known safety profile of aflibercept 2 mg and no dose relationship and no new safety signal was observed in the two studies.

The current study will investigate the efficacy and safety of aflibercept 8 mg with the intent of achieving non-inferior BCVA, while extending the dosing interval to reduce the number of injections and potentially improving visual and/or anatomic outcomes for aflibercept 8 mg vs. the currently approved aflibercept 2 mg dose regimen as well as maintaining the same safety profile as aflibercept 2 mg.

2.2 Background

In 2015, the global prevalence of any RVO, BRVO, and central CRVO in people aged between 30 and 89 years was 0.77% (95% confidence interval [CI] = 0.55 to 1.08), 0.64% (95% CI = 0.47 to 0.87) and 0.13% (95% CI = 0.08 to 0.21), equivalent to an overall of 28.06 million, 23.38 million and 4.67 million affected people (Song et al. 2019). Retinal vein occlusion may account for as much as 12% of severe vision loss and impacts a wide range of patients across ethnicities (Laouri et al. 2011). Patients of either sex are equally affected by RVO. While the prevalence of RVO increases with age and is most common in older patients, it also affects a large number of patients that are younger and of working age. The prevalence of RVO in people between the ages 30 and 59 years is 3.35 per every 1000 individuals. In fact, as many as 15% of patients with CRVO are less than 40 years of age (Rogers et al. 2010). Central retinal vein occlusion is associated with a worse prognosis than BRVO: severe vision loss and a higher risk of neovascular glaucoma (Holz et al. 2013).

The impact of vision loss on patient quality of life (QoL) is substantial. In a study of 51 patients with CRVO (5 bilateral), vision-related QoL (as measured by the National Eye Institute Visual Functioning Questionnaire-25 [NEI-VFQ-25] scoring algorithm) was significantly reduced in patients with CRVO compared with a reference group of patients without ocular diseases. Significant QoL detriments were seen in 11 out of 12 subscales (Deramo et al. 2003).

Patients with RVO often become dependent on caregivers to perform activities of daily living which can be particularly harmful to QoL for patients who live alone. Difficulty driving can pose important safety concerns for patients who depend on motor vehicles to travel to and from their place of employment. Importantly, patients with RVO report feeling social isolation which can lead to depression and further complications (Awdeh et al. 2010, Deramo et al. 2003). Before availability of IVT treatments, many patients experienced distress so substantial that they were willing to undergo invasive surgical treatment options.

Aflibercept 8 mg offers the potential for a similar efficacy benefit compared to aflibercept 2 mg, with a reduced number of IVT injections per time period. In addition, higher aflibercept

concentrations over a longer period of time may provide better visual outcomes and/or control of the anatomic features of RVO.

Refer to Section 4.2 for a discussion on the rationale for study design and Section 4.3 for dose justification.

This study will investigate the safety and efficacy of aflibercept 8 mg in macular edema secondary to RVO at treatment intervals of 48 weeks or longer.

2.3 Benefit/Risk Assessment

Aflibercept 2 mg is marketed for the treatment of adult 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. The efficacy and safety of aflibercept 2 mg used in adult patients with retinal diseases are well established; and its benefit-risk profile is considered favorable.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of aflibercept may be found in the Investigator's Brochure (IB).

2.3.1 Risk Assessment

The safety profile of aflibercept 8 mg is expected to be similar to that of the currently approved regimen of IVT aflibercept. Intravitreal injections, including those with Eylea®, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear, and iatrogenic traumatic cataract. Potential risks for aflibercept include embryo fetotoxicity and the development of arterial thromboembolic events (ATEs). For a dedicated assessment and categorization, a masked Anti-Platelet Trialists' Collaboration (APTC) adjudication committee will centrally evaluate all potential ATE reports in this study (see Section 10.1.6).

Pharmacokinetic (PK) and clinical safety data of IVT aflibercept have indicated that the known potential risks from systemic administration of anti-VEGF treatments in oncology indications were not identified with local treatment with IVT aflibercept. Studies performed with intravenous administration of aflibercept demonstrated that increases in blood pressure were the earliest pharmacodynamic indicator of systemic effects. Estimated exposure margins for free aflibercept after an 8 mg IVT dose, derived from linear extrapolation of available PK data for IVT-administered 2 mg IVT aflibercept, suggest adequate safety margins will be observed and maintained.

Nonclinical pharmacology evidence from the chronic DL-α-aminoadipic acid (DL-AAA) toxin induced leakage model in rabbits (Cao et al. 2018) and additional clinical extrapolation data collectively suggest that a higher dose of aflibercept could extend the dosing interval on average by approximately 2 half-lives (i.e., approximately 18 days) (see also Section 4.3) and thereby reduce the number of injections needed for successful treatment. In clinical trials, doses of up to 4 mg per eye in monthly intervals with injection volumes up to 100 µL and isolated cases of unintentional dosing with 8 mg per eye, which occurred in early studies of the development program of aflibercept 2 mg, were generally well tolerated in participants with nAMD. The efficacy and safety of aflibercept 8 mg has recently been demonstrated by the positive primary endpoint results of the ongoing Phase 2/3 PHOTON study in patients with DME and the ongoing Phase 3 PULSAR study in patients with nAMD. The safety

profile of aflibercept 8 mg in Phase 3 PULSAR study and Phase 2/3 PHOTON study were consistent with the known safety profile of aflibercept 2 mg and no new safety signals were observed in the 2 studies. Hence, with a safety profile expected to be consistent with aflibercept 2 mg, the overall risk/benefit profile for the 8 mg should be maintained or improved over the currently approved dose of aflibercept (Eylea® 2 mg) and for treatment of RVO. As risk minimization measures, participants and Investigators will be informed about the anticipated safety profile of 8 mg and exclusion criteria will be applied to account for potential safety concerns such as hypersensitivity, pregnancy, and uncontrolled hypertension.

Risk Assessment for Coronavirus Disease 2019 Pandemic:

There is currently an outbreak of respiratory disease (coronavirus disease 2019 [COVID-19]) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Appropriate medical measures have been implemented into this protocol to detect COVID-19 disease to confirm eligibility of participants and to safely conduct the study.

Aflibercept is a soluble decoy receptor fusion protein that has been shown to bind to VEGF-A, PlGF and VEGF-B, with subsequent blockade of activity demonstrated for VEGF-A and PlGF and is believed not to cause immune suppression.

Measures to mitigate the additional risks caused by COVID-19 are:

This study is going to start enrolling only when the Sponsor and contract research organization (CRO) in collaboration deem it is safe to start the study.

Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.

Once clinical signs of infection are reported by participants, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. Daily body temperature measurement is recommended.

The study intervention will not be administered to participants upon identification of any signs of COVID-19 infection.

Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on the Investigator's discretion. This would include serology testing at screening and virus testing prior to any admission.

The probability of virus transmission will be controlled as much as possible by:

- Advice for participant to adhere to local requirements for reduction of the public exposure while ambulatory.
- Participants are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, participants will be referred to the local health care system for further follow-up and treatment.
- Physical distancing and person to person contact restrictions will be applied during site visits and in-house confinement.
- Where physical distancing is not possible, personal protective equipment will be used by study participant (face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.

- Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

2.3.2 Benefit Assessment

Increasing the total amount of anti-VEGF therapeutic protein administered with a higher concentration formulation compared with currently available agents is a potential way to bring further benefits to participants with chorioretinal vascular diseases including nAMD, DME, and RVO. Delivering a larger amount of drug through a higher concentration formulation has the potential to increase the drug's biological duration of action and provide greater efficacy particularly in anatomic measures. This creates the potential not only for greater efficacy, but for reducing participant burden by extending the interval between IVT injections and consequently the overall number of doses. This reduction in the treatment burden is particularly important in this population where many participants are still working.

Aflibercept 8 mg may provide improved participant benefit through:

- Longer treatment intervals or longer for most participants after initial monthly dosing).
- Potential for improved visual, functional and/or anatomic efficacy.
- Lower injection-related risk over time.
- Increased participant compliance due to reduced treatment burden on participants, caregivers, physicians, and healthcare systems.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with aflibercept 8 mg are justified by the anticipated benefits that may be afforded to participants with macular edema secondary to RVO. More detailed information about the known and expected benefits and risks and reasonably expected AEs of aflibercept may be found in the IB.

3. Objectives, Endpoints, and/Estimands

Objectives	Endpoints
Primary	
• To determine if treatment with aflibercept 8 mg Q8W provides non-inferior BCVA change compared to aflibercept 2 mg Q4W	**Primary Endpoint:** • Change from baseline in BCVA measured by the ETDRS letter score at Week 36
Secondary - Efficacy	
• To determine if treatment with aflibercept 8 mg Q8W requires less injections compared to aflibercept 2 mg Q4W	**Key Secondary Endpoint** • Number of active injections from baseline to Week 64[1] **Secondary Endpoint** • Number of active injections from baseline to Week 36
• To determine the effect of aflibercept 8 mg Q8W compared to aflibercept 2 mg Q4W on other visual and anatomic measures of response	**Secondary Endpoints:** • Change from baseline in BCVA measured by the ETDRS letter score at Week 44[2] • Change from baseline in BCVA measured by the ETDRS letter score at Week 64 • Participant gaining at least 15 letters in BCVA from baseline at Weeks 36 and 64 • Participant achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen

Objectives	Endpoints
	equivalent) at Weeks 36 and 64 • Participant having no IRF and no SRF in the center subfield at Weeks 36 and 64 • Change from baseline in CST at Weeks 36 and 64
• To assess the efficacy of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W on vision-related QoL	• Change from baseline in NEI-VFQ-25 total score at Weeks 36 and 64
Secondary - Safety	
• To evaluate the safety of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W	• Occurrence of TEAEs and SAEs through Weeks 36 and 64
Secondary - Other	
• To evaluate duration of effect of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W	• Participants dosed only Q8W through Week 36 in the 8 mg Q8W group • Participant having last treatment interval ≥12 or of 16 weeks at Week 64 • Participant having next intended interval ≥12, ≥16 or of 20 weeks at Week 64
• To evaluate the PK of aflibercept 8 mg Q8W compared to aflibercept 2 mg aflibercept Q4W	• Systemic exposure to aflibercept as assessed by plasma concentrations of free, adjusted bound and total aflibercept from baseline through Weeks 36 and 64
Exploratory	
• To determine the effect of aflibercept 8 mg Q8W compared to aflibercept 2 mg Q4W on further visual and anatomic measures of response	• Change from baseline in BCVA measured by the ETDRS letter score at each visit • Participant with vision changes of at least 5, 10, or 15 letters in BCVA from baseline at each visit • Participant with no IRF and no SRF in the center subfield at each visit • Time to fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield) • Participant having sustained fluid-free retina over 36 and 64 weeks (total fluid, IRF, and/or SRF in the center subfield) • Change in area of retinal ischemia at Weeks 36 and 64 • Change in the area of fluorescein leakage at Weeks 36 and 64
• To study molecular drivers of RVO or related diseases, clinical efficacy of aflibercept, and affected molecular pathways	• Evaluation of clinical efficacy parameters by repertoire or frequency of genetic alterations (genomics substudy) • Treatment related changes in circulating biomarkers (FBR)

AE=adverse event, BCVA=best-corrected visual acuity, CST=central subfield thickness, ETDRS=early treatment diabetic retinopathy study, FBR=future biomedical research, IRF=intraretinal fluid, NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, PK=pharmacokinetics, QoL=quality of life, Q4W=every 4 weeks, Q8W=every 8 weeks, RVO=retinal vein occlusion, SAE=serious adverse event, SRF=sub-retinal fluid, TEAE=treatment-emergent adverse event

[1] Where premature treatment discontinue due to treatment related AE is considered as treatment-failure and the number of active injections from baseline to Week 64 is set to an unfavorable outcome (equal to 16, the maximum value).

[2] For the 8mg/5 and 2 mg groups only.

The primary estimand for the primary objective is described by the following attributes:

- Population: Adult participants with treatment-naïve macular edema secondary to RVO
- Endpoint: Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 36
- Treatment condition:
  - Aflibercept 8 mg administered with 3 initial every 4 weeks (Q4W) initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
  - Aflibercept 8 mg administered with 5 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
  - Aflibercept 2 mg administered Q4W until Week 32, followed by adjustment of treatment intervals according to treatment response

  A delayed active injection resulting in an injection interval up to 4 weeks longer than planned is considered to be in line with the treatment regimen of interest.
- Intercurrent events and strategies:
  - Premature treatment discontinuation – addressed by the hypothetical strategy (had participants continued treatment until Week 36)
  - Use of prohibited medication – addressed by the hypothetical strategy (had prohibited medications not been taken)
  - Missed study intervention:
    - Missed active injection resulting in an injection interval up to 4 weeks longer than planned: treatment policy strategy (the effect of a missed active injection will be included in the estimate of the treatment effect)
    - Missed active injection resulting in an injection interval more than 4 weeks longer than planned: hypothetical strategy (had injection not been missed or delayed by less than 4 weeks)
- Population-level summary: Difference in mean change from baseline to Week 36 in BCVA between each aflibercept 8 mg group and the aflibercept 2 mg group

Rationale for estimand: A hypothetical strategy is mainly used to address intercurrent events (especially premature treatment discontinuation) since the aim is to show non-inferiority (NI) of aflibercept 8 mg vs. aflibercept 2 mg and using a hypothetical strategy would be a conservative approach since it prevents the treatment arms from appearing more similar. For the intercurrent event “missed study intervention”, a missed sham injection has no impact on the endpoint as no active treatment was missed and thus it is not considered as additional intercurrent event. The impact of other potential intercurrent events is expected to be negligible. If a masked review will show an unexpected high number, the definition of the estimand may be complemented in the statistical analysis plan (SAP).

The secondary estimand for the secondary objective is described by the following attributes:

- Population: Adult participants with treatment-naïve macular edema secondary to RVO
- Endpoint: Number of active injections from baseline to Week 64 where premature treatment discontinuations due to treatment related AE is considered as treatment-failure and the number of injections is set to an unfavorable outcome (equal to 16, the maximum value)

- Treatment condition:
  - Aflibercept 8 mg administered with 3 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
  - Aflibercept 8 mg administered with 5 initial Q4W initiation doses followed by extension of treatment interval to 8-weeks and further adjustment of intervals according to treatment response
  - Aflibercept 2 mg administered Q4W until Week 32, followed by adjustment of treatment intervals according to treatment response

  The minimum treatment interval is 4 weeks while the study duration allows the maximum treatment interval to be 16 weeks. Imperfect adherence other than premature treatment discontinuation is considered as part of the treatment.
- Intercurrent events and strategies:
  - Premature treatment discontinuation
    - Due to lack-of-efficacy: Hypothetical strategy (had participants continued treatment until Week 64)
    - Due to treatment related AEs: Composite strategy (addressed in the endpoint definition)
    - Due to treatment unrelated AEs and other reasons: Hypothetical strategy (had participants continued treatment until Week 64)
  - Missed study intervention – addressed by treatment policy strategy (the effect of a missed active injection will be included in the estimate of the treatment effect)
- Population-level summary: Difference in mean number of active injections up to Week 64 between each aflibercept 8 mg group and the aflibercept 2 mg group

Rationale for estimand: Premature discontinuation due to treatment related AE; usually these participants would stop treatment. However, this would make it appear as if these participants had a reduced burden with respect to the number of injections. To mitigate this and to assign a penalty (since this is regarded as treatment failure) an unfavorable outcome equal to the maximum possible is assigned using the composite strategy. Premature discontinuation due to lack-of-efficacy is handled by the hypothetical strategy assuming that these participants would have continued study treatment with the maximum number of active injections possible with shortening of treatment interval in 4-week decrements (i.e., assuming they would meet the dose regimen modification (DRM) criteria for shortening at every dosing visit. For treatment unrelated AEs it is assumed that those participants could have continued in the study otherwise and behave similar to other participants in the study arm and hence addressed by the hypothetical strategy. Missed study intervention is regarded as part of clinical practice and hence addressed by the treatment policy strategy. The impact of other potential intercurrent events is expected to be negligible. If a masked review will show an unexpected high number, the definition of the estimand may be complemented in the SAP.

4. Study Design

4.1 Overall Design

This is a Phase 3, multi-center, randomized, double-masked, active-controlled clinical study to assess the efficacy and safety of high dose (8 mg) aflibercept administered IVT compared

to 2 mg aflibercept treatment in participants with treatment-naïve macular edema secondary to RVO.

The study population consists of men and women 18 years and older who have been diagnosed with macular edema secondary to RVO (BRVO, CRVO, or HRVO), involving the center of the macula, with a BCVA letter score of 73 to 24 (20/40 to 20/320) in the study eye.

Only 1 eye per participant will be enrolled in the study. If a participant's fellow (non-study) eye requires anti-VEGF treatment (for any approved indication in the respective country) during the participant's involvement in the study, the fellow eye should be treated with aflibercept 2 mg according to the approved treatment regimen in the respective country, irrespective of the randomization assignment of the participant. In countries where aflibercept 2 mg is not approved for treatment of RVO, the fellow eye may be treated with aflibercept 2 mg upon approval by an appropriate regulatory body and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) in the respective country. Otherwise, another locally approved treatment option should be used. The aflibercept 2 mg used for treatment of the fellow eye will whenever possible be provided by the Sponsor in compliance with local regulations. In cases where this supply is not possible, the costs of aflibercept 2 mg will be supported by the Sponsor in compliance with local regulations.

A total of approximately 822 eligible participants with macular edema secondary to RVO are planned to be randomized in a 1:1:1 ratio to aflibercept 8 mg every 8 weeks (Q8W) after 3 initial Q4W initiation doses group (8 mg/3) or aflibercept 8 mg Q8W after 5 initial Q4W initiation doses group (8 mg/5) or aflibercept 2 mg Q4W group (2 mg). A minimum of 40% of the eligible participants for each stratum CRVO or HRVO, and BRVO are planned to be included in this study. The randomization will be stratified by RVO type ([CRVO or HRVO] vs. BRVO), geographic region (Japan vs. Rest of Asia-Pacific [APAC] vs. America vs. Europe), and baseline BCVA (<60 vs. ≥60 letters). For the purpose of stratification by RVO type, HRVO participants will be included in the CRVO stratum.

The study consists of a screening/baseline period, a treatment period with duration of 60 weeks, and an end of study (EoS) visit at Week 64. No study intervention will be administered at the EoS visit at Week 64.

The DRM criteria are described in Sections 1.1 and 6.6 in detail.

An analysis of all data up to and including Week 36, including the analysis of the primary estimand, will be performed, once all participants have completed Week 36 (or prematurely discontinued). A final analysis of all data, including the analysis of the secondary estimand, will be conducted after all participants have completed the study at Week 64. Refer to Section 9.4 for detail.

This study includes an independent data monitoring committee (DMC) to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for efficacy, for harm, or for futility. Refer to Section 10.1.6 for detail.

4.2 Scientific Rationale for Study Design

The general participant population included in this study is considered to be representative of the population under treatment in the clinic, while the eligibility criteria minimize population variability and maximize the potential to measure clinically meaningful outcomes relevant to the study.

This study includes an active control group, rather than placebo/sham control. Aflibercept, administered according to a widely approved dose and regimen (2 mg, Q4W) is the active control, as this treatment regimen provides outcomes and an appropriate control for assessment of this high dose (8 mg) regimen.

This study uses a double-masked design, with sham procedures at visits where active study intervention is not scheduled, to prevent participant and Investigator bias during assessment of the safety and effectiveness of treatment.

The primary endpoint (change from baseline in BCVA measured by the ETDRS letter score at Week 36) was chosen as BCVA is a clinically relevant and well accepted measure of efficacy in clinical studies of participants with macular edema secondary to RVO.

The key secondary endpoint (number of active injections from baseline to Week 64) was chosen as number of active injections is a relevant measure of treatment burden in clinical studies of participants with macular edema secondary to RVO.

Anatomic measures of retinal thickness and retinal fluid are well-known markers of disease activity. These parameters are used by clinicians to determine treatment success and/or the timing of further re-treatment. These measures will be used as secondary endpoints in this Phase 3 study to help to determine the degree to which high dose (8 mg) can extend the dosing interval relative to aflibercept 2 mg. Additional endpoints are included to determine whether aflibercept 8 mg over a longer period of time may also provide potential additional functional benefits to participants with macular edema secondary to RVO.

4.3 Justification for Dose

Based on considerations of manufacturing capabilities, formulation, stability, and the likelihood of achieving a meaningful extension of the duration of effect, an 8 mg IVT dose is selected for evaluation in the present study.

The effects of increasing doses of aflibercept have been evaluated in a DL-AAA rabbit model of chronic retinal neovascularization and vascular leak. In these studies, in which rabbits received single IVT doses equivalent to up to 8 mg in humans, the duration of leak suppression was dose-dependent (Cao et al. 2018). In support of the 8 mg aflibercept clinical development program, the safety and toxicokinetic profiles of aflibercept were evaluated following IVT administration in a 26-week Good Laboratory Practice (GLP)-compliant toxicology study in cynomolgus monkeys. Aflibercept had no effect on clinical observations, body weights, qualitative food consumption, neurological examinations, heart rate, respiration rate, body temperature, pulse oximetry assessments, blood pressure, intraocular pressure (IOP), ocular photography, fluorescein angiography (FA), electroretinography, visual evoked potentials, jacketed external telemetry electrocardiogram. There were also no clear test article-related effects on clinical pathology parameters, macroscopic findings, or organ weights.

The aflibercept 8 mg IVT formulation is currently studied in 3 clinical studies in both nAMD and DME:

- A Phase 2 study (CANDELA), already completed, provided the first clinical data on safety, tolerability and efficacy of repeated doses of 8 mg aflibercept IVT injection for the treatment of nAMD. The results showed a similar safety profile to that of the 2 mg aflibercept dose with positive trends in fluid resolution and vision improvement.

- A Phase 3 study (PULSAR) is ongoing and investigating the safety, tolerability and efficacy of repeated doses of 8 mg aflibercept IVT injection for the treatment of nAMD.
- A Phase 2/3 study (PHOTON) is ongoing and investigating the safety, tolerability and efficacy of repeated doses of 8 mg aflibercept IVT injection for the treatment of DME.

Prior to the initiation of the aforementioned dedicated clinical studies investigating 8 mg IVT aflibercept, the safety of aflibercept 4 mg was investigated in Phase 1 and 2 clinical studies for the treatment of nAMD (VGFT-OD-0502, VGFT-OD-0508, and VGFT-OD-0603) and for the treatment of DME (VGFT-OD-0512). Also, 3 patients in the VGFT-OD-0603 study were unintentionally dosed with 8 mg. In the post-marketing safety database for aflibercept, 43 cases of PPD (dosing at greater than 2 mg per eye) have been reported, with 27 patients reported to have received at least 1 dose of 2 to 4 mg, 3 patients 8 mg (one of them 4 mg bilateral), and in 6 patients more than 8 mg. In the remaining cases the specific dose is unknown. Overall, a similar safety profile to that reported for a 2 mg dose was observed. There was no indication of dose-related systemic anti-VEGF effects such as blood pressure increase, proteinuria or increased frequency of ATEs.

With the expectation of longer dosing interval, resulting in a lower number of injections, similar safety profile and relatively small increase in injection volume, the 8 mg dose was selected for evaluation in this study.

The Phase 3 studies of Eylea® 2 mg in CRVO and BRVO employed Q4W dosing until the primary endpoint, and showed continuous gain in vision until that time point when 6 monthly injections had been administered. By using a similar Q4W dosing regimen until the primary endpoint as a comparator, this study sets the highest possible standard of efficacy, to enable a robust evaluation of the NI of aflibercept 8 mg in terms of vision outcomes when administered less frequently than 2 mg. In order to evaluate the efficacy and safety of aflibercept 8 mg in the treatment of RVO, and assess different levels of reduction in treatment burden, the initial Q4W dosing for the aflibercept 8 mg arm will be limited to 5 or 3 injections Q4W, depending on assignment at randomization. Thereafter, the injection interval will be extended to 8 weeks until the primary endpoint, to provide convenient treatment regimens which progressively reduce treatment burden while aiming to achieve non-inferior efficacy and comparable safety to that obtained with monthly 2 mg (see Section 6.6).

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the schedule of activities (SoA) (Section 1.3).

The end of the study as a whole is defined as the date of the last visit of the last participant in the study in all centers of all participating countries.

5. Study Population

The study population consists of men and women 18 years and older who have been diagnosed with treatment-naïve macular edema secondary to RVO (BRVO, CRVO, or HRVO), involving the center of the macula, with a BCVA letter score of 73 to 24 (20/40 to 20/320) in the study eye.

Only 1 eye per participant will be enrolled in the study as the study eye. For participants who meet eligibility criteria in both eyes during the screening phase, the eye with the worse BCVA

letter score or worse prognosis will be the study eye. If both eyes have the same BCVA letter score, the eye with the clearest lens and ocular media will be selected as the study eye. If there is no objective basis for selecting the study eye, factors such as ocular dominance (better focus ability), other ocular pathology and participant preference should be considered in making the selection. The final selection will be done by the Investigator at baseline and must not be changed during the course of the study. The non-study eye, is then considered as the "fellow eye". The non-study eye (fellow eye) should be treated by the Investigator as per local standards/guidelines. The participants' eligibility to take part in the study in terms of ocular imaging assessments will be reconfirmed by the central reading center.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply **at both screening and baseline visits**, except where otherwise indicated:

Age

1. Adult ≥18 years of age (or country's legal age of adulthood if the legal age is >18 years) at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Treatment-naïve macular edema involving the foveal center secondary to RVO (BRVO, HRVO, or CRVO) diagnosed within 16 weeks (112 days) **before the screening visit** in the study eye.
3. Early Treatment Diabetic Retinopathy Study BCVA letter score of 73 to 24 (20/40 to 20/320) **at screening and baseline visits** in the study eye.
4. Decrease in BCVA determined to be primarily the result of RVO in the study eye.
5. Mean CST ≥300 µm on optical coherence tomography (OCT) if excluding Bruch's membrane (e.g., Cirrus or Topcon) or ≥320 µm if including Bruch's membrane (e.g., Heidelberg Spectralis), confirmed **by the reading center at the screening visit and by the site at baseline visit** in the study eye.

Informed Consent

6. Capable of giving signed informed consent form (ICF) as described in Section 10.1.3 by study participant or legally acceptable representative, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
7. US participants will be required to have a Health Insurance Portability and Accountability Act (HIPAA) authorization; in other countries, as applicable according to national laws.

Contraception

8. Women of childbearing potential (WOCBP) or men who are sexually active with partners of childbearing potential must agree to use highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 4 months after the last administration of study intervention. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for participation in clinical studies and fulfil the conditions set on Section 10.4.2.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply **at either screening or baseline visit**, except where otherwise indicated:

Medical Conditions – Per Eye

1. 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.
2. Any ocular disorders that, in the opinion of the Investigator, may confound interpretation of study results in the study eye.
3. Presence or history of the following ocular conditions:
    a. Advanced age-related macular degeneration (neovascular AMD or geographic atrophy) in the study eye.
    b. Diabetic macular edema or diabetic retinopathy, defined in diabetic participants as diabetic retinopathy lesions outside the area of the vein occlusion in the study eye and anywhere in the retina in the fellow eye.
    c. Anterior segment neovascularization, vitreous hemorrhage, retinal detachment in the study eye.
    d. Vitreomacular traction, epiretinal membrane or structural damage to the macula that is considered by the Investigator to significantly affect central vision or preclude improvement in vision in the study eye.
    e. Macular hole of stage 2 and above in the study eye.
    f. Myopia of a spherical equivalent of at least 8 diopters prior to any refractive or cataract surgery in the study eye.
    g. Corneal transplant or corneal dystrophy in the study eye.
    h. Idiopathic or autoimmune uveitis in the study or in the fellow eye.
4. Presence of the following ocular conditions **at screening or baseline visit**:
    a. Significant media opacities, including cataract, that interfere with BCVA, or imaging assessments (e.g., fundus photography [FP], OCT) in the study eye.
    b. Aphakia, or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium-aluminum-garnet [YAG] posterior capsulotomy performed more than 30 days before **the screening visit**), in the study eye.
    c. Uncontrolled glaucoma (defined as IOP >25 mmHg despite treatment with anti-glaucoma medication); or history or likely future need of glaucoma surgery in the study eye.
    d. Intraocular inflammation/infection (including trace, or above, cells in the anterior chamber and/or vitreous) within 12 weeks (84 days) of **the screening visit** in the study or in the fellow eye.
    e. Extraocular or periocular infection or inflammation (including infectious blepharitis, keratitis, scleritis, or conjunctivitis) in the study or in the fellow eye.

Medical Conditions – Per Participant

5. Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg) **at the screening visit or baseline visit**.
6. Uncontrolled diabetes mellitus, defined by hemoglobin A1c (HbA1c) >12% **at the screening visit**.
7. History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) before **the screening visit or between screening and baseline visits**.
8. Renal failure requiring dialysis, or renal transplant at screening or potentially during the study.
9. Known allergy or hypersensitivity to any of the compounds/excipients in the study interventions formulations, including fluorescein used in FA.
10. Presence of any contraindications indicated in the locally approved label for aflibercept.
11. Systemic infection at the time of screening or baseline. Or systemic treatment for suspected or active systemic infection **at screening or baseline visit**.
12. Pregnant or breastfeeding women.
13. 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, might affect interpretation of the results of the study, renders the participant at high risk from treatment complications or is likely to interfere with full participation in the study as detailed in the SoA (Section 1.3).
14. Members of the clinical site study team and/or his/her immediate family.

Prior Therapy

15. Any prior or concomitant ocular or systemic treatment (with an investigational or approved, anti-VEGF or other agent) or surgery for RVO in the study eye.
16. Previous administration of systemic anti-angiogenic medications for any condition.
17. Prior treatment of the study eye with any of the following drugs (any route of ophthalmic administration) or procedures:
    a. Anti-angiogenic drugs at any time including investigational therapy (e.g., with anti-angiopoietin/anti-VEGF bispecific monoclonal antibodies).
    b. Previous use topical steroids within 4 weeks (28 days) from **the screening visit**, or intraocular or periocular steroids within 16 weeks (112 days) from **the screening visit**, or steroid implants at any time.
    c. Previous treatment with intraocular or periocular implant, gene therapy, or cell therapy at any time.
    d. Treatment with ocriplasmin at any time.
    e. Vitreoretinal surgery (including scleral buckling) at any time.
    f. Any intraocular surgery, including cataract surgery, within 12 weeks (84 days) before **the screening visit**.
    g. Previous treatment with retinal laser photocoagulation.

18. Prior treatment of the fellow eye with any of the following:
    a. Gene therapy, or cell therapy in the fellow eye at any time.
19. Any concomitant ocular or systemic administration of drugs that may interfere with or potentiate the mechanism of action of aflibercept.

Prior/Concurrent Clinical Study Experience

20. Participation in other clinical studies requiring administration of investigational treatments (other than vitamins and minerals) at the time of **screening visit**, or within 30 days or 5 half-lives of administration of the previous study intervention, whichever is longer.

5.3 Lifestyle Considerations

No lifestyle restrictions are required during the study.

5.4 Screen Failures and Re-screening

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Re-starting the defined set of screening procedures to enable a "screening failure" participant to re-screen at a later time point is not allowed, with the following exceptions:

- The participant had successfully passed the screening procedures but was not randomized and could not start subsequent treatment on schedule.
- The inclusion/exclusion criteria preventing the participant's initial attempt to participate have been changed (via protocol amendment).
- The reason for the screening failure (e.g., uncontrolled glaucoma or arterial hypertension, or initial screening occurred too early to fulfil the requirements for time intervals after specific therapeutic interventions specified in the exclusion criteria) was subsequently resolved.

Under any of the above exceptions, a participant may be re-screened once only. To be eligible, the re-screened participant must meet all inclusion criteria and none of the exclusion criteria at the baseline and re-screening visit. In any case, the Investigator must ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk. Also, for re-screening, the participant must re-sign the ICF, even if it was not changed since the participant's previous screening.

Re-screened participants will receive a new subject number.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), sham, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

Study visits will be scheduled Q4W throughout the study duration. At every visit until Week 60, the participants will receive an active or sham injection for masking purposes.

Table 6–1: Study Intervention(s) Administered

Group Name	Aflibercept 8 mg	Aflibercept 2 mg	Sham	Diagnostic Agents
Intervention Name	Aflibercept 8 mg	Aflibercept 2 mg	Sham	Fluorescein sodium 100 mg/mL
Type	Drug	Drug	Not applicable	Dye
Dose Formulation	Solution in vial	Solution in vial	Not applicable	Solution in vial
Unit Dose Strength(s)	114.3 mg/mL	40 mg/mL	Not applicable	Not applicable
Dosage Level(s)	8 mg (70 µL)	2 mg (50 µL)	Not applicable	500 mg (5 mL)
Route of Administration	IVT injection	IVT injection	Not applicable	Intravenous injection
Use	Experimental	Active comparator	Sham procedure	Diagnostic
IMP/AxMP	IMP	IMP	IMP	AxMP
Packaging and Labeling	Study Intervention will be provided in sterile 3 mL glass vials. Each vial will be labeled as required per country requirement.	Study Intervention will be provided in sterile 2 mL glass vials. Each vial will be labeled as required per country requirement.	Empty kit	Sites will use locally available commercial product in unchanged market packaging, used according to the approved label.

AxMP=auxiliary medicinal product (medicinal products used in the context of a clinical trial but not as investigational medicinal product), IMP=investigational medicinal product, IVT=intravitreal(ly)

Aflibercept 2 mg for the fellow eye treatment (Section 6.9.1) is considered an auxiliary medicinal product (AxMP) in this study.

Each vial is for single use only.

6.1.1 Medical Devices

Medical devices used in this study include both devices that help prepare and deliver the study intervention, as well as devices that are used to gather additional clinical data. These devices are conformité européenne (CE) marked (or the Food and Drug Administration [FDA] cleared) according to the regulatory requirements specific for the country where the study site is located.

The Sponsor provides an 18-gauge filter needle for use preparing the study medication in this study. Other medical devices (not manufactured by or for Bayer) to be used in this study to deliver the medication according to Table 6–1 include syringes and injection needles. Instructions for use of these medical devices are provided by the legal manufacturer of these devices. Deficiencies (including malfunctions, use error, and inadequate labelling) related to the filter needles, injection needles, and syringes shall be documented and reported to the Sponsor by the Investigator throughout the clinical investigation (see Section 8.4.7) so they can be appropriately managed by the Sponsor.

Additional devices are used for gathering additional clinical data (measuring blood pressure, IOP, heart rate). Instructions for use of these medical devices are provided by the legal

manufacturer of these devices. Deficiencies related to these devices should be reported directly to the legal manufacturer of the deficient medical device.

6.2 Preparation, Handling, Storage, and Accountability

The Investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The institution Investigator, the head of the institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Investigator site file, if applicable.

The study intervention will be supplied in kits that include the following:

- Sterile study intervention in sealed glass vials (see Table 6–1)
- Filter needle (18-gauge)

Study intervention is to be stored in the refrigerator (2°C to 8°C) and must not be frozen. The vials must be kept in the outer carton to protect them from light. When study intervention is removed from the refrigerator, the solution should be inspected visually and it should have no evidence of turbidity. If participants, cloudiness, or discoloration are visible, the vial must not be used. Study medication can withstand brief exposures to temperatures up to 25°C, such as those that may occur during finishing, shipping, and handling, without compromising either the physical or chemical stability or the potency of the protein. Sham kits will assigned for visits requiring sham procedures. The sham kits are empty but should be handled same as a study intervention kit. Sham procedure will be given on visits when an active injection is not planned.

Details on the administration of aflibercept IVT injection, sham procedure, and post-injection procedures are provided in Section 10.7.

After study intervention injection or sham procedure, participants will be observed for at least 30 minutes.

Dose regimen modification procedures are detailed in Section 6.6.

Fluorescein 100 mg/mL solution for injection is a dye that makes the retinal vessels visible during FA examinations, and as such, it will be used as an AxMP in this periodic ophthalmic examination. This medicine is for diagnostic use only. It is not used to treat any condition. Fluorescein 100 mg/mL solution for injection will be purchased by each site as locally available commercial product and will be used according to the approved label.

Above described guidance in terms of appropriate conditions during transit, authorized site staff handling and accountability will also apply to AxMPs. Regarding storage, fluorescein does not require any special temperature storage conditions. Should not be kept in the

refrigerator or freezer. The vial should be kept in the outer carton in order to remain protected from light. Once open the vial must be used immediately. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles and the container and its closure are undamaged.

6.3 Assignment to Study Intervention

Participants will be randomly assigned in a 1:1:1 ratio to 1 of 3 parallel treatment groups as described in Section 4.1. The randomization will be stratified by RVO type ([CRVO or HRVO] vs. BRVO), geographic region (Japan vs. Rest of APAC vs. America vs. Europe), and baseline BCVA (<60 vs. ≥60 letters), to ensure balanced distribution of the treatment groups within each stratum.

Participants will be centrally assigned to randomized study intervention using an Interactive Response Technology (IRT). Before the study is initiated, the directions for the IRT will be provided in the Study Reference Manual. To accomplish random assignments, computer-generated randomization lists will be provided by the study Sponsor or delegate and provided to the IRT vendor. Before the study is initiated, the log-in information and directions for the use of the IRT will be provided to each site.

Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3).

6.4 Masking

All study site personnel (except for those performing the unmasked roles as described below and in Table 6–2), must remain masked to treatment assignment of participants in order to ensure an unbiased assessment of visual acuity, safety, and ancillary study measures. Masking will continue until the end of the study. Masking/unmasking of the study team will be described in a masking maintenance plan. An unmasked monitor will be responsible for unmasked site visits and will be unmasked to study intervention. Participants, all other study personnel, and central reading center must remain masked to treatment assignment. A masked monitor will be responsible for the masked site visits. Site personnel must not change from unmasked to masked roles after the first participant is randomized at the site. Masked staff are allowed to change to unmasked role under exceptional circumstances, if approved by the Sponsor. Active and sham treatments will be masked and will be administered by an unmasked Investigator (or designee).

Masked Roles

The masked personnel are responsible to (i) assess AEs (except for the post-injection evaluation), (ii) perform the masked assessment of efficacy and safety, (iii) assess if a participant has met pre-specified criteria for dose regimen shortening or extension, (iv) report any medical device AEs/serious adverse events (SAEs)/device deficiencies relating to devices used for gathering clinical data (see Section 6.1.1). Depending on their function, masked personnel are also responsible for performing the masked assessments of visual acuity, ophthalmologic assessments, non-ophthalmologic assessments, and blood samples collection and laboratory assessments. Every effort will be made to ensure that the visual acuity examiner remains masked to treatment assignment in order to allow for an unbiased assessment of visual acuity. The visual acuity examiner should only perform the assigned task of visual acuity assessments and should make every effort to remain masked to participant's

previous letter score and study eye; another masked team member will document BCVA values in source and electronic case report form (eCRF).

Unmasked Roles

An unmasked Investigator (or designee), separate from the masked personnel, will perform active injection/sham procedure, post-injection indirect ophthalmoscopy, and post-injection IOP assessment. The participant must remain unaware of the treatment assignment; thus, the study intervention and syringe must be covered and remain unidentifiable to the participant. The unmasked Investigator will not have any role in the study beyond the (i) receipt, tracking, preparation, destruction, and administration of study intervention, and (ii) reporting any AEs or medical device AEs/SAEs/device deficiencies relating to the filter needle, injection needle, or syringe, during the post-injection period. An unmasked drug handler (e.g., pharmacist) may be assigned to handle receipt, storage, and preparation of active and sham kits. Unmasked personnel are also allowed to do screening/baseline procedures such as initial informed consent (reconsent must be undertaken by masked personnel). All individuals performing unmasked roles must be trained for maintenance of the masking measures required in the context of this study. An overview of the masked and unmasked site personnel is presented in Table 6–2.

Table 6–2: Masked and Unmasked Site Personnel

Study Procedure	Masked Study Staff[a]	Unmasked Study Staff[b]	Certification Needed
Study intervention:			
Study intervention accountability		X	
Injection-related procedures:			
IRT access[c]	X	X	
(Pre-)injection procedures		X	
IVT injection (active, sham)		X	
Post-injection assessment (post-injection indirect ophthalmoscopy, and post-injection IOP)		X	
AE reporting:			
AEs and device-related AEs/SAEs/deficiencies relating to filter needle, injection needle, or syringe during injection procedure and post-injection assessment		X	
All other AEs, device-related AEs/SAEs/deficiencies for devices used for gathering clinical data	X		
Ophthalmic assessment:			
BCVA examination BCVA recording in eCRF (different from BCVA examiner)	X X		X
Full ophthalmic examination (IOP, slit lamp, indirect ophthalmoscopy)	X		
FA, FP	X		X
SD-OCT	X		X
OCT-A, if applicable	X		X
NEI-VFQ-25 questionnaire	X		X

Study Procedure	Masked Study Staff[a]	Unmasked Study Staff[b]	Certification Needed
Other procedures:			
Informed consent	X[d]	X[d]	
Demography, medical and ocular history	X[d]	X[d]	
Record concomitant medications/treatments/interventions[e]	X		
Blood sampling (e.g., serum pregnancy test, PK sampling)	X		
Blood pressure measurement	X		
Urine pregnancy test	X		

AE=adverse event, BCVA=best corrected visual acuity, eCRF=electronic case report form, FA=fluorescein angiography, FP=fundus photography, IOP=intraocular pressure, IRT=Interactive Response Technology, IVT=intravitreal, NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, OCT-A=optical coherence tomography angiography, PK=pharmacokinetic, SAE=serious adverse event, SD-OCT=spectral domain optical coherence tomography.

a. Includes masked Investigator, masked study nurse/study coordinator, and study personnel for ocular assessments.
b. Includes, unmasked Investigator administering active/sham study intervention and assessing post-injection ocular assessments, and drug handler/pharmacist dispensing active/sham study intervention.
c. For the purpose of treatment assignments/kit numbers, only the unmasked staff should have access to IRT. Masked staff will have limited access to IRT.
d. Masked or unmasked personnel are allowed to do screening/baseline procedures such as initial informed consent. Reconsent must be undertaken by masked personnel.
e. Except concomitant medications due to AE occurring during the injection or in the immediate post-injection period, which must be reported by unmasked Investigator.

Masked study intervention kits coded with a medication numbering system will be used. In order to maintain the mask, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct. In compliance with applicable regulations, in the event of a suspected unexpected serious adverse reactions (SUSAR) (see Section 8.4.4) related to the masked treatment, the participant's treatment code will usually be unmasked before reporting to the health authorities, ethics committees and Investigators (Section 10.3.5).

Emergency Unmasking

The IRT will be programmed with mask-breaking instructions. In case of an emergency, the Investigator has the responsibility for determining if unmasking of a participant's intervention assignment is warranted. If the Investigator is unavailable, and a treating physician not associated with the study requests emergency unmasking, the emergency unmasking requests are forwarded to the study specific emergency medical advice 24 hours/7 day service. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unmasking is warranted, the Investigator should make every effort to contact the Sponsor prior to unmasking a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unmasked, the Sponsor must be notified within 24 hours after breaking the mask. The date and reason that the mask was broken must be recorded in the source documentation and eCRF, as applicable.

Emergency Medical Contacts:

The contact details for the Emergency Medical Contacts will be provided in the Study Manual and the Investigator (Site) File. Medical Monitor names, contact information, and country-specific toll free numbers will be included.

6.5 Study Intervention Compliance

Study intervention will be administered by a qualified ophthalmologist. Details of aflibercept injection will be recorded in the eCRF (e.g., time of injection, type of anesthesia, treatment site). An adequate record of receipt, dispensing and destruction of all study intervention must be captured on the dispensing log and / or in the IRT.

6.6 Dose Regimen Modification

Study visits will be scheduled Q4W throughout the study duration. At every visit until Week 60, the participants will receive an active or sham injection for masking purposes. During the first 32 weeks, the 2 mg group will receive an active injection at every visit while the 8 mg groups will initiate treatment with injections Q4W for a total of 3 doses or will initiate treatment with injections Q4W for a total of 5 doses, followed by extension of the treatment interval of 8 weeks. Beginning at Week 36 through Week 60, treat and extend (T&E) will be employed for the 2 mg and 8 mg/3 groups and beginning at Week 44 through Week 60 for the 8 mg/5 group. Extension or shortening of the dosing interval will depend on meeting DRM criteria. The DRM criteria may also indicate active injections for the 8 mg groups at Weeks 20 (8 mg/3) and 28 (8 mg/3 and 8 mg/5) for participants in the need of a treatment (Figure 1-1).

DRM Shortening Criteria:

Beginning at Week 16 for the 8 mg/3 group, Week 24 for the 8 mg/5 group and Week 40 for the 2 mg group, participants will be eligible to have their dosing interval shortened by 4 weeks if both the following DRM shortening criteria are met **at a dosing visit**:

1. Best-corrected visual acuity loss >5 letters from reference visit*, AND
2. >50 µm increase in CST from reference visit*

   *Reference visits are Week 12 for the 8 mg/3 group, Week 20 for the 8 mg/5 group and Week 20 for the 2 mg group.

For example, in case the DRM shortening criteria are met at Week 16, participants will have their following dosing intervals shortened to 4 weeks, thus, will receive additional active doses at Weeks 20 and 28 and remain on 4-week intervals until end of study or DRM criteria for interval extension are met. In case the DRM shortening criteria are met at Week 24, participants will receive an additional active dose at Week 28 and remain on 4 week intervals until end of study or DRM criteria for interval extension are met. The minimum planned interval between dosing visits is 4 weeks. The actual interval between injections may be shorter than 28 days due to the allowed visit windows. Once a participant has their treatment interval shortened to Q4W, they will continue to be treated Q4W until end of study or DRM criteria for extension are met, as described below.

DRM Extension Criteria Starting at Weeks 32 and 40:

Starting at Week 32 for the 2 mg and 8 mg/3 groups, and starting at Week 40 for the 8 mg/5 group, participants will be eligible for interval extension (by 4-week increments) if both the following DRM extension criteria are met **at a dosing visit**:

1. Best-corrected visual acuity loss <5 letters from reference visit*, AND
2. CST thickness <320 µm if including Bruch's membrane (e.g., Heidelberg Spectralis), or <300 µm if excluding Bruch's membrane (e.g., Cirrus or Topcon) on OCT

*Reference visits are Week 12 for the 8 mg/3 group, Week 20 for the 8 mg/5 group and Week 20 for the 2 mg group.

When these criteria are met at a dosing visit, the participant receives the planned dose at that visit and has the next treatment interval extended by 4 weeks (e.g., if the last interval was 4 weeks, the next will be 8 weeks). If at a later dosing visit the DRM extension criteria are met again, the participant receives the planned dose at that visit and the next interval will be extended by another 4 weeks (e.g., if the last interval was 8 weeks, the next will be 12 weeks).

For the assessment of DRM shortening and extension criteria, in case the measurement is not available at the reference visit, the most recent measurement from previous visit should be used instead. For example, if reference visit is Week 12 and this measurement is not available, the Week 8 measurement should be used instead. If both Weeks 12 and 8 measurements are not available, the Week 4 measurement should be used instead. In case there are no measurements at Weeks 4, 8, and 12, the participant will be considered non-compliant and discontinued from the study.

For participants who do not meet the criteria for shortening or extension of the interval, the current dosing interval will be maintained.

All assessments of DRM criteria will be performed by Investigator evaluations of BCVA and OCT examinations. The same model of OCT machine must be used for individual participants throughout the study to provide comparable measurements.

6.7 Continued Access to Study Intervention after the End of the Study

Considering the broad availability of approved treatments for RVO, intervention will not be supplied after the end of the study. Participants will not be restricted with regard to pursuing available approved treatments for RVO.

6.8 Treatment of Overdose

For this study, any dose of study intervention greater than 2 mg (for the group receiving low dose of Eylea®) or 8 mg (for the group receiving high dose of Eylea®) per injected eye will be considered an overdose.

Once the fellow eye receives aflibercept 2 mg therapy during the study, any dose of Eylea® greater than 2 mg for the fellow eye will be considered an overdose.

Overdosing with increased injection volume may increase IOP. In these cases, evaluation of IOP and central retinal artery perfusion should be performed immediately after the injection and monitored until normalized. If there is severe elevation of IOP causing disruption of central retinal artery perfusion, immediate performance of an anterior segment paracentesis should be considered.

In the event of an overdose, the Investigator should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the overdose in the eCRF, recording to the possible extent the amount of the dose administered.
- Contact the Medical Monitor as soon as possible.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.9 Concomitant Therapy

For prohibited drugs and procedures prior to the study, including treatments in either the study eye or the fellow eye, see Section 5.2.

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

If a pretreatment concomitant medication is administered in the study eye before injection (e.g., antibiotic or anesthetic), it must be administered for sham and fellow eye injections as well.

6.9.1 Prohibited Medications and Procedures

Study Eye:

Participants may not receive any standard or investigational agents for treatment of their macular edema secondary to RVO in the study eye other than assigned study treatment as specified in this protocol until they have completed the EoS/early discontinuation visit assessments. This includes medications administered locally (e.g., IVT, by juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating the study eye or the fellow eye.

Fellow Eye:

Only 1 eye per participant may be enrolled in the study. If a participant's fellow (non-study) eye requires anti-VEGF treatment during the participant's involvement in the study, the fellow eye should be treated with aflibercept 2 mg according to the approved treatment regimen in the respective country, irrespective of the randomization assignment of the participant. In countries where aflibercept 2 mg is not approved for treatment of RVO, the fellow eye may be treated with aflibercept 2 mg upon approval by an appropriate regulatory body and IRB/IEC in the respective country. Otherwise, another locally approved treatment option should be used. The aflibercept 2 mg used for treatment of the fellow eye will whenever possible be provided by the Sponsor in compliance with local regulations. In cases where this supply is not possible, the costs of aflibercept 2 mg will be supported by the Sponsor in compliance with local regulations.

Although the fellow eye can receive treatment, it will not be considered an additional study eye. Participants who receive treatment for the fellow eye should remain in the study. Treatment of the fellow eye will be documented in the eCRF Concomitant Medication page. Safety for the fellow eye will be monitored; AEs/SAEs will be reported in the eCRF. Once the fellow eye receives aflibercept 2 mg therapy during the study, AEs will be assessed as related/not related to "aflibercept 2 mg (fellow eye)" in addition to being assessed as related/not related to the study intervention delivered to the study eye (aflibercept 2 mg), IVT aflibercept injection procedure, and other protocol-specified procedures. Any dose of Eylea® greater than 2 mg for the fellow eye will be considered an overdose.

Non-Ocular (Systemic):

Non-ocular (systemic) standard or investigational treatments for macular edema secondary to RVO of the study or fellow eye are not permitted.

6.9.2 Permitted Medications and Procedures

Any medication considered necessary for the participant's welfare, and that is not expected to interfere with the evaluation of the study intervention, may be given at the discretion of the Investigator.

Any medication or vaccine (including any sedation, anesthesia, eye drops used for the study procedures, blood-derived products, prescription or over-the-counter medicines, probiotics, vitamins, and herbal supplements) that the participant receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

If a pre-treatment concomitant medication is administered in the study eye before injection (e.g., antibiotic, topical anesthetic), it must be administered for sham procedures as well. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Study intervention discontinuation can be triggered by the participant (or legally authorized representative) or by the treating Investigator.

Participants for whom study intervention is planned at any time during the study but not administrated will be considered to have temporarily discontinued study intervention. If study intervention is temporarily discontinued, it can be restarted at any time during the study.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety evaluation, but study intervention **cannot** be restarted at any time during the study. Participants who only finish the baseline visit, but missed all the following 3 visits at Weeks 4, 8, and 12 will be considered non-compliant and permanently discontinued.

See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant who discontinues study participation prematurely for any reason is defined as a discontinuation if the participant has already been randomized.

A participant may withdraw from 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, or compliance reasons. This is expected to be uncommon.

Participants must be withdrawn from the study if any of the following occurs:

- Relevant laboratory abnormality or SAEs, if the Sponsor or Investigator sees this as medical reason to warrant withdrawal.

- AE (ocular or nonocular) that, from the participant's or the Investigator's view, is potent 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.
- A female participant becomes pregnant. Refer to Section 8.3.5.
- Lost to follow-up. Refer to Section 7.3.
- Decision by the Sponsor to halt the entire study.

Participants may be withdrawn from the study if any of the following occurs:

- Any treatment for RVO other than study interventions in the study eye is considered a prohibited treatment, and participant must be withdrawn from the study.
- Systemic anti-angiogenic agents were taken by the participant during the study.
- If, in the Investigator's opinion, continuation of the study would be harmful to the participant's well-being.
- At the specific request of the Sponsor and in liaison with the Investigator (e.g., obvious noncompliance or safety concerns).

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Participants who withdraw from the study will not be replaced.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Participants should be seen for all visits on the designated day, with an allowed "visit window" as indicated in the SoA. Any unscheduled visits (e.g., for safety follow-up) must be documented in the eCRF.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 78 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General/Baseline Procedures

8.1.1 Eligibility Criteria

All inclusion and exclusion criteria (Sections 5.1 and 5.2) will be reviewed by the Investigator or designee to ensure that the participant qualifies for the study. Recheck of clinical status will need to be performed before the first dose of study intervention in the SoA (Section 1.3).

8.1.2 Demography

The following demographic information will be recorded:

- Age, sex
- Ethnic origin (1: Japanese; 2: Hispanic/Latino; 3: Other)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Height, without shoes (cm)
- Body weight, without shoes (kg)
- Body mass index (BMI) (kg/m^2)

8.1.3 Medical History

A medical history will be obtained by the Investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed that the Investigator considers to be clinically relevant.

8.2 Efficacy Assessments

Planned timepoints for all assessments are provided in the SoA (Section 1.3).

8.2.1 Ophthalmic and General Examinations

Note: In this section, all ophthalmic examinations are described, irrespective of whether they are used for efficacy or safety assessments.

Ophthalmic evaluations will be conducted according to the SoA (Section 1.3).

All ophthalmic examinations are to be conducted pre-injection in both eyes and post-injection in the study eye only, unless indicated otherwise.

At any visit, ophthalmic examinations not stipulated by this protocol may take place outside of this protocol at the discretion of the Investigator.

8.2.1.1 Best Corrected Visual Acuity

Visual function will be assessed using the ETDRS protocol (Early Treatment Diabetic Retinopathy Study Research Group. 1985) starting at 4 meters. Refraction is to be done at each visit.

Visual acuity examiners must be certified to ensure consistent measurement of BCVA. Any certified and trained study personnel may perform this assessment (including but not limited to ophthalmologist, optometrist, or technician). For each participant, the same examiner should perform all assessments whenever possible. Best-corrected visual acuity should be done before any other ocular procedures are performed.

8.2.1.2 Slit Lamp Examination

Slit lamp examination will be performed bilaterally.

Participants' anterior eye structure and ocular adnexa will be examined bilaterally (pre-dose on visits with active injection) at each study visit using a slit lamp by the masked Investigator as specified in Table 6–2.

8.2.1.3 Intraocular Pressure

Intraocular pressure will be measured using Goldman applanation tonometry, rebound tonometry Icare, or Tonopen and the same method of measurement must be used for each participant throughout the study.

At all visits, IOP should be measured bilaterally by the masked Investigator (or designee). On days when study intervention is administered, IOP should also be measured approximately 30 to 60 minutes (±10 minutes so measure should be at least 20 minutes after IVT injection and no more than 70 minutes after IVT injection) after administration of study intervention (study eye only) by the unmasked Investigator (or designee). The exact timing is left to the discretion of the unmasked Investigator.

If multiple post-injection measurements are performed, the final measurement before the participant leaves should be documented in the eCRF. Any injection-related increase in IOP (and treatment) should be documented in a masked fashion.

8.2.1.4 Spectral Domain Optical Coherence Tomography

Retinal and lesion characteristics will be evaluated using spectral domain optical coherence tomography (SD-OCT). Technicians must be masked to treatment assignment and must be certified by the reading center to ensure consistency and quality in image acquisition and segmentation. For all visits where the SD-OCT procedure is scheduled, images will be captured and read by the technician and Investigator for individual treatment decisions and sent to an independent reading center where images will be read by masked readers. The participants' eligibility to take part in the study in terms of SD-OCT will be reconfirmed by the central reading center. The same SD-OCT imaging system used at screening and Day 1 must be used at all follow-up visits in each participant. Images will be taken in both eyes before dosing (active or sham injection). All SD-OCTs will be archived electronically by the study sites as part of the source documentation. The study manual will further specify the acquisition and assessment for OCT during the study.

8.2.1.5 Optical Coherence Tomography Angiography

Optical coherence tomography angiography is optional at all sites that have the relevant equipment. Technicians must be masked to treatment assignment and must be certified by the reading center to ensure consistency and quality in image acquisition. If optical coherence tomography angiography (OCT-A) cannot be performed at the screening visit, it may be done at baseline visit. The same imaging modality used at screening must be used at all follow-up visits in each participant. Images will be taken in both eyes before dosing (active or sham injection).

All OCT-As will be archived electronically by the study sites as part of the source documentation. The study manual will further specify the acquisition and assessment for OCT-A during the study.

8.2.1.6 Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed according to local medical practice and applicable medical standards at the site.

Participants' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre-dose (bilateral) by the masked Investigator and post-dose (study eye) by the unmasked Investigator, as specified in Table 6–2. Post-dose evaluation should be performed as soon as possible, approximately 0 to 15 minutes after injection. The exact timing is left to the discretion of the unmasked Investigator. If the indirect ophthalmoscopy cannot be performed immediately after injection, see Section 10.7.2.3.

8.2.1.7 Fundus Photography and Fluorescein Angiography

The anatomical state of the retinal vasculature of the study eye will be evaluated by FP and FA at visits specified in Table 6–2. The treating Investigator may perform additional FA/FP at other times during the study based on his/her medical judgment and standard of care. Photographers must be masked to treatment assignment and must be certified by the reading center to ensure consistency and quality in image acquisition.

Fundus photography and FA images will be read by the Investigator for individual treatment decisions and sent to an independent reading center where images will be read by masked

readers. The participants' eligibility to participate in the study in terms of FA will be confirmed by the central reading center before randomization.

The same FA/FP imaging system used at screening and Day 1 must be used at all subsequent visits in each participant. Images will be taken in both eyes before dosing (active or sham injection). Detailed instructions can be found in the imaging manual.

All FA and FP images will be archived electronically by the site as part of the source documentation.

The study manual will further specify the acquisition and assessment for FA/FP during the study.

8.2.1.8 National Eye Institute Visual Functioning Questionnaire-25

Vision-related QoL will be assessed using the NEI-VFQ-25 questionnaire (Mangione et al. 2001) in the interviewer-administered format. It is a reliable and valid 25-item version of the 51-item NEI-VFQ.

National Eye Institute Visual Functioning Questionnaire-25 to be administered in a quiet room by a masked study-related person trained to administer this type of questionnaire, preferably before other visit procedures are performed.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Physical Examinations

A routine physical examination will assess cardiovascular, respiratory, gastrointestinal, and neurological systems and will follow the standard practice of the site. Body weight, height, and BMI should be measured at Visit 1 (screening). The assessment will be based on the clinical judgment of the Investigator and aim to evaluate the overall health of the participant.

8.3.2 Vital Signs

Body temperature, blood pressure, and heart rate will be measured per the procedure outlined in the study manual.

Vital signs should be measured prior to injection and any blood sampling. Timing of all blood pressure assessments should be within 2 hours of clock time of dosing on Day 1.

Where possible, blood pressure assessments will be taken using a calibrated automated office blood pressure with the Omron Model HEM 907XL (or comparable). Measures will be recorded in the eCRF. Detailed instructions can be found in the study manual.

Clinically significant abnormal findings will be reported as AEs in the eCRF.

8.3.3 Electrocardiograms

A standard digital 12-lead electrocardiogram (ECG) will be performed. Heart rate will be recorded from the ventricular rate and the PR, QRS, RR, and QT intervals will be recorded. The ECG strips or report will be retained with the source documentation. Electrocardiograms will be forwarded to a central reader.

8.3.4 Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. All samples collected for laboratory assessments

should be obtained prior to administration of fluorescein, and prior to administration of study intervention.

The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or repetition of these analyses is not considered to provide clinically relevant information.

- If clinically significant/any values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.5 Pregnancy Testing

Pregnancy testing is not required for women of non-childbearing potential. For women of childbearing potential (WOCBP), a negative pregnancy test is required at screening (serum) and baseline (urine), and well as at every subsequent visit (urine) (see the SoA in Section 1.3).

Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.

Pregnancy test results will be recorded in the eCRF.

8.4 Adverse Events, Serious Adverse Events and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

The definitions of device-related safety events, adverse device effects (ADEs), and serious adverse device effects (SADEs) can be found in Section 10.6. Device deficiencies are covered in Section 8.4.7.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All (S)AEs will be collected from the moment when informed consent is obtained until the last follow-up visit at the timepoints specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs, and the procedures for completing and transmitting SAE reports, are provided in Section 10.3.

For participants receiving fellow eye injections, AEs will also be assessed as related/not related to “aflibercept 2 mg (fellow eye)” in addition to being assessed as related/not related to the study drug delivered to the study eye (aflibercept 2 mg/aflibercept 8 mg treatment), IVT injection-procedure, and other protocol-specified procedures.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

For all studies except those using medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.4.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 90 days after the last dose of study intervention.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

8.4.6 Adverse Events of Special Interest

Adverse events of special interest (AESI) have to be reported to the Sponsor along the timelines set for SAEs (even though they may not be classified as serious), i.e., within 24 hours of the Investigator's awareness, as described in Section 10.3.3.

Adverse events of special interest are:

Arterial thromboembolic events as defined by the APTC adjudication committee criteria include nonfatal myocardial infarction, nonfatal ischemic stroke, nonfatal hemorrhagic stroke, or death resulting from vascular or unknown causes.

8.4.7 Medical Device Deficiencies

Medical devices are being provided by or on behalf of the Sponsor for use in this study. To fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.6.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.6 of the protocol.

8.4.7.1 Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the Investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

The method of documenting medical device deficiencies is provided in Section 10.6.

8.4.7.2 Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.4.7.3 Prompt Reporting of Device Deficiencies to the Sponsor

Device deficiencies will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device deficiency.

The Medical Device Deficiency Report Form will be sent to the Sponsor by emailing the completed product technical complaint form (see Section 8.4.7).

The Sponsor will be the contact for the receipt of device deficiency reports.

8.4.7.4 Regulatory Reporting Requirements for Device Deficiencies

The Investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The Investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5 Pharmacokinetics

For the investigation of systemic exposure to aflibercept, blood samples will be collected for measurement of plasma concentrations of aflibercept (bound and free) as specified in the SoA (Section 1.3). Sparse PK sampling will be performed in all participants.

A maximum of 7 samples may be collected at additional timepoints during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of sampling, may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of study intervention.

Details about the collection, processing, storage and shipment of samples will be provided separately (e.g., sample handling sheets or laboratory manual).

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

8.7.1 Optional Genomic Substudy

Optional participation in genomic substudy will be offered to all participants. Substudy is not applicable for China. Collection of blood samples for optional genomic substudy is contingent upon approval by an appropriate regulatory body in the respective country, if applicable. Participants who do not wish to participate in the optional genomic substudy may still participate in the main study. See Section 10.5 for details.

8.8 Future Biomedical Research

Participation is optional. Participants who do not wish to participate in the future biomedical research (FBR) component of the study may still participate in the main study. Substudy is not applicable for China. No additional blood sample is required – analysis may be performed on remaining blood samples (from e.g., PK sampling). Samples will be banked in long-term storage. The unused PK samples will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for FBR of RVO, related diseases or pathways blocked by study intervention, and any adverse reactions that may emerge. These samples may also be used for unrelated assay development and validation purposes. After 15 years, any residual samples will be destroyed. The results of these FBR analyses will not be presented in the clinical study report.

8.9 Biomarkers

Not applicable.

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The SAP will be finalized prior to unmasking and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.1 Statistical Hypotheses

The one-sided test hypotheses in relation to the primary and two-sided test hypotheses in relation to the secondary estimands, see Section 3, are described according to the fixed hierarchical order planned for their testing.

1. First test problem (related to the primary estimand):

   Null hypothesis H_{01}: $\mu_{1.5} \leq \mu_0 - 4$ vs. alternative hypothesis H_{11}: $\mu_{1.5} > \mu_0 - 4$

Where $\mu_{1.5}$ and μ_0 represent the group means for the change from baseline in BCVA at Week 36 for the 8 mg/5 group and the 2 mg group, respectively.

Note that larger values measured for the change from baseline in BCVA are better. The aim is to show that the 8 mg/5 group is no less effective than the existing the 2 mg group, using a NI margin of 4 letters for the difference of the means.

2. Second test problem (related to the primary estimand):

   Null hypothesis H_{02}: $\mu_{1.3} \leq \mu_0 - 4$ vs. alternative hypothesis H_{12}: $\mu_{1.3} > \mu_0 - 4$

   Where $\mu_{1.3}$ and μ_0 represent the group means for the change from baseline in BCVA at Week 36 for the 8 mg/3 group and the 2 mg group, respectively.

   Note that larger values measured for the change from baseline in BCVA are better. The aim is to show that the 8 mg/3 group is no less effective than the existing the 2 mg group, using a NI margin of 4 letters for the difference of the means.

3. Third test problem (related to the secondary estimand):

   Null hypothesis H_{03}: $f_3(Y_1|X) = g(Y_2|X)$ vs. alternative hypothesis H_{13}: $f_3(Y_1|X) \neq g(Y_2|X)$

   Where $f_3(Y_1|X)$ and $g(Y_2|X)$ represent the conditional distributions for the number of active injections from baseline to Week 64 for the 8 mg/3 group and the 2 mg group, respectively.

   Note that smaller values for the number of active injections are better. The aim is to show that the 8 mg/3 group is superior to the existing the 2 mg group in that it leads to less injections. Thus, the null hypothesis should be rejected in favor of the alternative hypothesis and the estimate of the treatment effect based on a linear regression model adjusted for the stratification variables should favor the 8 mg/3 group.

4. Fourth test problem (related to the secondary estimand):

   Null hypothesis H_{04}: $f_5(Y_1|X) = g(Y_2|X)$ vs. alternative hypothesis H_{14}: $f_5(Y_1|X) \neq g(Y_2|X)$

   Where $f_5(Y_1|X)$ and $g(Y_2|X)$ represent the conditional distributions for the number of active injections from baseline to Week 64 for the 8 mg/5 group and the 2 mg group, respectively.

   Note that smaller values for the number of active injections are better. The aim is to show that the 8 mg/5 group is superior to the existing the 2 mg group in that it leads to less injections. Thus, the null hypothesis should be rejected in favor of the alternative hypothesis and the estimate of the treatment effect based on a linear regression model adjusted for the stratification variables should favor the 8 mg/5 group.

5. Fifth test problem (related to the primary estimand):

   Null hypothesis H_{05}: $\mu_{1.5} \leq \mu_0$ vs. alternative hypothesis H_{15}: $\mu_{1.5} > \mu_0$

   Where $\mu_{1.5}$ and μ_0 represent the group means for the change from baseline in BCVA at Week 36 for the 8 mg/5 group and the 2 mg group, respectively.

   Note that larger values measured for the change from baseline in BCVA are better. The aim is to show that the 8 mg/5 group is superior to the existing the 2 mg group.

6. Sixth test problem (related to the primary estimand):

   Null hypothesis H_{06}: $\mu_{1.3} \leq \mu_0$ vs. alternative hypothesis H_{16}: $\mu_{1.3} > \mu_0$

   Where $\mu_{1.3}$ and μ_0 represent the group means for the change from baseline in BCVA at Week 36 for the 8 mg/3 group and the 2 mg group, respectively.

   Note that larger values measured for the change from baseline in BCVA are better. The aim is to show that the 8 mg/3 group is superior to the existing the 2 mg group.

Justification for NI margin:

As described in Section 4.2 and similarly to the other ongoing studies for development of aflibercept 8 mg, BCVA will be quantified through ETDRS letter scores. The ETDRS charts used for this examination consist of 14 lines of decreasing size where each line includes 5 letters of similar size, such that every third line represents a halving of the visual angle. Differences in ETDRS letter score smaller than a single line (5 letters) are therefore not commonly considered to be clinically relevant. For this reason, a NI margin of 4 letters has already been accepted for use in other indications in the aflibercept 8 mg program.

Based on the integrated analysis of the two sham-controlled Phase 3 studies GALILEO and COPERNICUS in CRVO participants, the point estimate of the treatment effect for the change from baseline in BCVA at Week 24 was CCI CCI for aflibercept 2 mg vs. sham. The observed change from baseline at Week 24 for Eylea 2 mg was 17.7 letters CCI . The observed change from baseline at Week 24 in VIBRANT in BRVO patients was of similar magnitude (17.0 letters [SD=11.9]). In these studies, Eylea 2 mg was administered Q4W until Week 24. Similarly, in the current Phase 3 study, a Q4W regimen is also used for Eylea 2 mg, albeit until Week 36. Therefore, it seems reasonable to assume that the treatment effect for Eylea 2 mg at Week 36 would at least be of similar magnitude. Additionally, a similar patient population (based on inclusion/exclusion criteria) as in the former studies is planned to be enrolled and the primary endpoint will be assessed similarly (BCVA as measured by EDTRS). Therefore, in summary, the presence of assay sensitivity, i.e., the ability of the study to show, if sham would be included as control, that the treatment effect for Eylea 2 mg is of similar size as seen in previous studies (as described in International Council for Harmonisation [ICH] E10 and FDA Guidance on NI studies) can be deduced.

Using the lower bound of the 95% CI of the treatment effect estimate from the integrated analysis of GALILEO and COPERNICUS and assuming that the treatment effect at Week 24 is similar to the treatment effect at Week 36, a conservative estimate of the assumed treatment effect vs. sham in the 2 mg group would be CCI letters for the planned Phase 3 study. Using a NI margin of 4 letters in the planned study then means that at least CCI CCI) of the assumed treatment effect in the 2 mg group should be retained in the 8 mg group.

9.1.1 Multiplicity Adjustment

A hierarchical testing procedure will be used to control the overall family-wise type I error in the strong sense. The statistical comparisons will be carried out in the hierarchical order as defined for the hypotheses in Section 9.1. Consequently, the second, third, fourth, fifth, and sixth null hypotheses will only be tested if the previous comparisons were in favor of the 8 mg/5 group or 8 mg/3 group in that the previous null hypotheses were rejected and, for two-sided null hypotheses only, the related estimator supported a superiority of the corresponding 8 mg arm. Operationally the hypotheses will be evaluated by one-sided tests or

two-sided tests with a significance level of 0.025 or 0.05, respectively, estimating two-sided 95% CIs for the treatment difference.

9.2 Analysis Sets

For the purpose of analysis, the following analysis sets are defined:

Table 9–1: Analysis Sets

Participant Analysis Set	Description
Full analysis set (FAS)	All participants randomly assigned to study intervention.
Safety analysis set (SAF)	All participants randomly assigned to study intervention who were exposed to study intervention at least once.
Pharmacokinetic analysis set (PKS)	All participants randomly assigned to study intervention with at least one non missing PK result after the first dose of study intervention.

PK=pharmacokinetic

The Full analysis set (FAS) is used to analyze endpoints related to the efficacy objectives and the Safety analysis set (SAF) is used to analyze the endpoints and assessments related to safety.

9.3 Statistical Analyses

9.3.1 General Considerations

The testing of the primary and secondary endpoints is performed at an overall significance level of 0.25 for the one-sided tests and 0.05 for the two-sided tests, respectively. The testing strategy is defined in Section 9.1.1. For descriptive purposes 95% two-sided CIs will be provided where applicable.

More details (including any subgroup analyses) will be described in the SAP.

9.3.2 Primary Endpoint Analysis

9.3.2.1 Definition of Endpoint(s)

The primary endpoint is the change from baseline in BCVA (as measured by ETDRS letter score) at Week 36.

9.3.2.2 Main Analytical Approach

For the primary analysis of the primary efficacy variable, a mixed model for repeated measurements (MMRM) will be used with baseline BCVA measurement as a covariate and treatment group and the stratification variables as fixed factors as well as terms for the interaction between baseline and visit and for the interaction between treatment and visit. A Kenward-Roger approximation will be used for the denominator degrees of freedom. Further, an unstructured covariance structure will be used. If the model does not converge, an appropriate covariance structure will be used instead.

$$Y_{ijk} = \beta_0 + x_i \times \beta_{base} + \beta_{type}^{(t)} + \beta_{reg}^{(l)} + \beta_{base\_cat}^{(m)} + \beta_{treat}^{(k)} + \beta_{visit}^{(j)} + x_i \times \beta_{base*visit}^{(j)} + \beta_{treat*visit}^{(k,j)} + \epsilon_{ijk}$$

with

- Y_{ijk} being the change from baseline to visit j for the participant i receiving treatment k

- β_0 being the intercept
- x_i being the baseline BCVA measurement of participant i
- β_{base} the fixed effect of the baseline BCVA measurement
- $\beta_{type}^{(t)}$ the fixed effect of RVO type t
- $\beta_{reg}^{(l)}$ the fixed effect of region l
- $\beta_{base\_cat}^{(m)}$ the fixed effect of categorized baseline BCVA measurement m
- $\beta_{treat}^{(k)}$ the fixed effect of treatment k
- $\beta_{visit}^{(j)}$ the fixed effect of visit j
- $\beta_{base*visit}^{(j)}$ the interaction between baseline BCVA and visit j
- $\beta_{treat*visit}^{(k,j)}$ the interaction between treatment k and visit j
- ϵ_{ijk} the residual error with $\epsilon_{ijk} \sim N(0, \sigma_{jk}^2)$ and $corr(\epsilon_{ijk}, \epsilon_{ij'k}) = \rho^k\_\{j, j'\}$

In terms of the model parameters the population-level summary for the primary estimand (i.e., the treatment effect at Week 36) can then be expressed as

$$D = \left[\beta_{treat}^{(8mg)} + \beta_{treat*visit}^{(8mg,w36)}\right] - \left[\beta_{treat}^{(2mg)} + \beta_{treat*visit}^{(2mg,w36)}\right]$$

The primary analysis will be performed using the FAS. Participants will be analyzed within their original randomized group (regardless of any changes to dose interval). In line with the primary estimand and approach to the intercurrent event of premature treatment discontinuation, no explicit imputation of missing BCVA measurements will be performed. Missing BCVA measurements will be assumed to be missing at random and will be handled by the MMRM model.

Further details will be specified in the SAP.

9.3.2.3 Sensitivity and Supplementary Analysis

The analysis of the primary endpoint will be repeated to take into account important protocol deviations with the potential to affect efficacy as a supplementary analysis, whereby having an important protocol deviation that could be deemed to affect primary efficacy is also classed as an intercurrent event (in addition to the incurrent event of premature treatment discontinuation), and addressed by the hypothetical strategy. The analysis will use the FAS and include all data points obtained at or after randomization up to the earliest date of discontinuation of investigational intervention or important protocol deviation potentially affecting efficacy. Additional supplementary and sensitivity analyses may be described in the SAP.

9.3.3 Secondary Endpoints Analysis

9.3.3.1 Secondary Efficacy Endpoints

For the analysis of the key-secondary endpoint (number of active injections from baseline to Week 64) a non-parametric rank analysis of covariance (non-parametric rank ANCOVA) as described in Stokes et al. 2012 will be carried out to adjust the comparison of the treatment groups for the stratification variables. In addition to the assessment of the treatment effect based on the non-parametric ANCOVA, an estimate of the treatment effect based on a linear

regression model adjusted for the stratification variables will be provided. Additional supplementary and sensitivity analyses may be described in the SAP.

Secondary efficacy endpoints that are not part of the hierarchical testing procedures described in Section 9.1 will only be analyzed descriptively. Continuous variables may be analyzed by similar repeated measurement models as for the primary endpoint, if applicable. Binary endpoints may be analyzed by Cochran-Mantel-Haenszel methodology.

Nominal two-sided 95% CIs and p-values may be provided.

Details will be provided in the SAP.

9.3.3.2 Secondary Safety Endpoints

Adverse events will be analyzed for the SAF.

Treatment-emergent adverse events and SAEs will be summarized through Weeks 36 and 64.

Definitions

Treatment-emergent adverse events are defined as AEs that occurred in the time frame from first injection (active or sham) to the last injection (active or sham) plus 30 days.

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®).

The number and percentage of participants in the SAF with at least one treatment-emergent adverse event (TEAE)/treatment-emergent SAE will be summarized by System Organ Class (SOC) and Preferred Term (PT).

9.3.3.3 Other Secondary Endpoints

9.3.3.3.1 Pharmacokinetics Data

Pharmacokinetics data may be analyzed for the Pharmacokinetic analysis set (PKS). The concentrations of free, adjusted bound, and total aflibercept over time will be summarized by descriptive statistics for each treatment group. Concentrations may be further grouped by factors such as age, renal function, hepatic function, concomitant medications, body weight, ethnicity, etc. No formal statistical hypothesis testing will be performed.

Pharmacokinetic and exposure-response analysis may be performed using population approaches (popPK and popPK/PD, e.g., by non-linear mixed effect modeling). Such evaluations will be described in a separate analysis plan and will be reported separately. Such evaluations may be started prior to database lock. If this is applicable, appropriate measures will be taken to maintain masking of the study team, e.g., data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

9.3.4 Other Safety Analyses

All other safety variables will be analyzed for the SAF by descriptive methods.

9.3.4.1 Vital Signs

Vital signs (temperature, heart rate, and blood pressure) will be summarized by baseline and absolute change from baseline to each scheduled assessment time with descriptive statistics, for the SAF.

9.3.4.2 Laboratory Tests

Laboratory data will be analyzed for the SAF.

Laboratory test results will be summarized by baseline and absolute change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of participants with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

9.3.5 Other Analysis

9.3.5.1 Exploratory Endpoints

Exploratory endpoints will only be analyzed descriptively. Continuous variables will be analyzed by similar repeated measurement models as for the primary endpoint. Binary endpoints will be analyzed by Cochran-Mantel-Haenszel methodology.

Nominal two-sided 95% CIs and p-values may be provided.

Details will be provided in the SAP. Additional exploratory endpoints may be specified in the SAP.

9.4 Interim Analyses

No interim analyses in the sense of a group-sequential or adaptive design are planned.

An analysis of all data up to and including Week 36, including the analysis of the primary estimand, will be performed, once all participants have completed Week 36 (or prematurely discontinued).

A final analysis of all data, including the analysis of the secondary estimand, will be conducted after all participants have completed the study at Week 64 (or prematurely discontinued).

Additional details will be provided in the SAP.

9.5 Sample Size Determination

The sample size calculation is based on the primary efficacy estimand and its endpoints, change from baseline in BCVA measured by the ETDRS letter score at Week 36.

The sample size has been calculated under the following assumptions for the 8 mg/5 group and the 2 mg group:

- The changes in BCVA letter score from baseline are normally distributed.
- The true difference in the mean change in BCVA between the 8 mg/5 group and the 2 mg group is 0 letters.
- The standard deviation is CCI [redacted]).

Similar assumptions have been made for the 8 mg/3 group and the 2 mg group.

A sample size of 246 evaluable participants per group provides approximately 90% power for rejecting the null hypotheses for both the first and second test problem in the hierarchal order, see Section 9.1, with a 1-sided t-test at a significance level of 0.025.

Approximately 10% of the participants are assumed to drop out before Week 36 (the time point of the primary endpoint). Therefore, approximately 274 participants are to be randomized in each group, leading to a total sample size of approximately 822 participants.

To facilitate a supportive exploratory subgroup analysis for BRVO and CRVO/HRVO, a minimum of 40% of the participants, i.e., 329 participants, per RVO type ([CRVO or HRVO] vs BRVO) are targeted to be randomized. With this sample size, there is approximately a 90% probability (given the assumptions mentioned above) that the 95% CI for the difference between pooled aflibercept 8 mg vs. aflibercept 2 mg excludes a margin of 5 letters in each subgroup.

Intercurrent Events

Premature treatment discontinuation of study treatment (for any reason) is defined as an intercurrent event. The primary estimand will follow the hypothetical strategy and as such will determine the treatment effect in the hypothetical scenario that all participants continued with randomized treatment until Week 36.

Justification of Japanese Sample Size

In past aflibercept studies, no differences in response have been identified between the Japanese and the global study population, establishing that aflibercept (along with other drugs in the same anti-VEGF IVT Injection drug class) is ethnically insensitive (ICH Topic E5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data and related FDA Guidance dated Sep 2006). Approximately 10% of the study participants are planned to be recruited in Japan, to allow appropriate representation in the overall study population and each subgroup.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted reviewed and approved in accordance with national legislation and undergo scientific and ethical assessment before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH GCP and national and international regulations.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants or their legally authorized representative and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. They or their legally authorized representatives will be required to sign a statement of informed consent that

meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study, if the changes may be relevant to the subject's willingness to continue participation in the trial, in accordance with ICH GCP 4.8.2.

A copy of the ICF(s) must be provided to the participants or their legally authorized representative.

A new ICF is required if a participant is re-screened.

A separate ICF will address the use of remaining samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4 Recruitment strategy

Recruitment of participants will be the responsibility of the study's clinical sites. Where permissible, additional measures will be put in place to increase the awareness to the study. These may include posters, flyers, contacts through referral networks, advertisements and others.

Detailed description of the recruitment strategy will be provided in country-specific documentation as required.

10.1.5 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records, datasets or biological samples 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.

Participants 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

Participants 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/IEC members, and by inspectors from regulatory authorities.

The contract between Sponsor and study sites specifies responsibilities of the parties related 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.

10.1.6 Committees Structure

10.1.6.1 Independent Data Monitoring Committee

An independent DMC will meet periodically to review the ongoing safety of participants in the study and to provide recommendations to continue or terminate the study depending upon these reviews. The operation of the independent DMC is governed by a charter that describes the group's frequency of meeting, procedures (including but not limited to periodic safety monitoring), and requirements for reporting its observations to the Sponsor.

10.1.6.2 Anti-Platelet Trialists' Collaboration Adjudication Committee

Potential ATEs will be evaluated by a masked adjudication committee according to criteria formerly applied and published by the APTC prior to database unmasking (Antithrombotic Trialists' Collaboration 1994, Antithrombotic Trialists' Collaboration 2002). Arterial thromboembolic events as defined by the APTC criteria include nonfatal myocardial infarction, nonfatal ischemic stroke, nonfatal hemorrhagic stroke, or death resulting from vascular or unknown causes. The committee will include at least two cardiologists and the provision of data and activities of the committee will be governed by a charter.

10.1.7 Dissemination of Clinical Study Data

Bayer fulfills its commitment to publicly disclose study results through posting the result of the studies on public registries in accordance with applicable law and regulations.

Result Summaries of Bayer's Sponsored clinical studies in drug development Phases 2, 3 and 4 and Phase 1 studies in participants are provided in the Clinical Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition results of clinical drug trials will be provided on the publicly funded website ClinicalTrials.gov and European Union (EU) Clinical Trials Register in line with the applicable regulations.

In accordance with the current EU regulation, result summaries will be submitted within one year from the end of the studies in adult populations or within 6 months for studies in pediatric population, in **all** participating countries. No preliminary data analysis (e.g., on EU data only) will be performed, as this might compromise data integrity and the scientific validity of the study. Bayer commits to sharing upon request from qualified scientific and medical researchers participant-level clinical study data, study-level clinical study data, and protocols from clinical studies in participants for medicines and indications approved in the United States (US) and EU on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical studies are considered for publication in the scientific literature irrespective of whether the results of the clinical studies are positive or negative.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of case report forms (CRFs) will be provided in eCRF Completion Instructions.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Source Data Location List (SDLL) or equivalent.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this. It is the expectation of the Sponsor that all data have source documentation available at the site.

The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, 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 currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10 Study and Site Start and Closure

Study Start

The study start date is the date on which the clinical study will be open for recruitment of participants.

The start of a clinical study in EU is defined as the date on which the first site is declared by the Sponsor to be ready to enroll in a country and clinical study will be open for recruitment of participants.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IEC/IRB, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10–1 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the

same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10–1: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters		
Hematology	• Hemoglobin • Hematocrit • Platelet count • RBC count	• RBC indices ➢ MCV ➢ MCH ➢ %Reticulocytes	
	• WBC count with differential: ➢ Neutrophils ➢ Lymphocytes ➢ Monocytes ➢ Eosinophils ➢ Basophils		
Clinical Chemistry	• Albumin • Alkaline phosphatase • ALT/SGPT • AST/SGOT • BUN • Calcium • Carbon dioxide • Chloride	• CPK • Creatinine • Glucose (non-fasting) • HDL • LDH • LDL • Potassium • Sodium	• Total and direct bilirubin • Total cholesterol • Total protein, serum • Triglycerides • Urea (or BUN) • Uric acid • HbA1c
Routine Urinalysis	• Specific gravity, color, clarity, crystals • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)		
Pregnancy Testing	• Highly sensitive serum hCG pregnancy test at screening and baseline (urine), and well as at every subsequent visit (urine) (as needed for WOCBP)[1]		
Other screening tests	• FSH (as needed in women of non-childbearing potential only) • The results of each test must be entered into the eCRF		

ALT=alanine amino transferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CPK=creatine phosphokinase, eCRF=electronic case report form, FSH=follicle-stimulating hormone, HbA1c=hemoglobin A1c hCG=human chorionic gonadotropin, HDL=high density lipoprotein, IEC=Independent Ethics Committee, IRB=Institutional Review Board, LDH=lactate dehydrogenase, LDL=low density lipoprotein, MCH=mean corpuscular hemoglobin, MCV=mean corpuscular volume, RBC=red blood cell, SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamic-pyruvic transaminase, WBC=white blood cell, WOCBP=women of childbearing potential
NOTES:
[1] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of Adverse Event

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdoses should be reported regardless of sequelae.
- Sign, symptoms, or the clinical sequelae of suspected medication errors, misuse and abuse of either study intervention or a concomitant medication. Medication errors, misuse and abuse per se will not be reported as an AE/SAE, unless it is resulting in AE/SAE. Such medication errors, misuse and abuse should be reported regardless of sequelae.
- Lack-of-efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the Adverse Event Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2 Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose, meets the one or more of the criteria listed:

a. **Results in death**

b. **Is life-threatening**

- The term life-threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

f. **Is a suspected transmission of any infectious agent via an authorized medicinal product**

g. **Other situations:**

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

- An ocular important medical event may include the following:
  - An AE that requires either surgical or medical intervention to prevent permanent loss of vision
  - Substantial, unexplained vision loss or an AE that causes substantial vision loss

10.3.3 Definition of Adverse Event of Special Interest

Events Meeting the AESI Definition:

- Arterial thromboembolic events (ATEs) including cerebrovascular ischemic events (such as cerebrovascular accident, transient ischemic attack) and cardiovascular ischemic events (such as myocardial infarction, coronary heart disease).

10.3.4 Recording and Follow-Up of Adverse Events and Serious Adverse Events and Adverse Event of Special Interest

Adverse Event, Serious Adverse Event, and Adverse Event of Special Interest Recording

- When an AE/SAE/AESI occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE/AESI information.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AESI.

Assessment of Intensity

- The Investigator will make an assessment of intensity for each AE, SAE, and AESI reported during the study and assign it to one of the following categories:
  - Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
  - Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/AESI. The Investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator **mus**t review and provide an assessment of causality for each AE/SAE/AESI and document this in the medical notes.

  There may be situations in which an SAE/AESI has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission** of the SAE/AESI data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE/AESI follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs, SAEs, and AESI

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE, SAE, or AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of Serious Adverse Event and Adverse Event of Special Interest

SAE and AESI Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE/AESI to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE/AESI data transmission (see next section) to report the event within 24 hours.
- The site will enter the SAE/AESI data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE/AESI from a study participant or receives updated data on a previously reported SAE/AESI after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- Contacts for SAE/AESI reporting can be found in the safety reporting gateway.

SAE/AESI Reporting via Paper Data Collection Tool

- Email transmission of the SAE/AESI paper data collection tool is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE/AESI data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE/AESI data collection tool within the designated reporting timeframes.
- Contacts for SAE/AESI reporting can be found in Investigator site file.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1 Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are considered WOCBP (fertile)

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below):
    - A postmenopausal state is defined as no spontaneous menstruation for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.4.2 Contraception Guidance

Female participants must be either of non-child bearing potential or use a highly effective method of contraception. This applies from the time of ICF signature until at least 4 months after the last administration of study intervention.

Highly effective contraceptive measures include:

- 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.
- Intrauterine device (IUD); intrauterine hormone releasing system (IUS).
- Bilateral tubal ligation.
- Vasectomized partner or vasectomized study participant.
  - Must have received medical assessment of the surgical success.
- Sexual abstinence.†‡

  †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 interventions. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

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

10.5 Appendix 5: Genetics

Genetic predisposition that might be associated with treatment response to aflibercept and/or disease progression will be investigated as a voluntary genomic substudy.

- The participation in the genomic substudy is voluntary and has no influence on the participation in the main study.

- A whole blood sample will be obtained from those participants, who have signed a separate ICF for genomic substudy. The sample may be used as source of germline DNA.
- DNA sample will be utilized for genotyping of candidate genes suggested to play a role in retinal diseases and may include analysis of the entire genome (utilizing methodologies such as whole exome sequencing combined with dense single nucleotide polymorphism arrays) for discovery of new variants.
- Genomic analyses may include sequencing of the candidate genes and allele specific polymerase chain reaction (PCR) analyses, for example. The methods will be chosen according to current state of the art utilizing analytically validated assays.
- Details on the collection and handling of samples will be provided in separate documents (e.g., sample handling sheets or laboratory manual), available at the Investigator Site File.
- Results will be reported separately (e.g., in a biomarker evaluation report).

10.6 Appendix 6: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, Serious Adverse Device Effects and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the Investigator and the Sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to the medical devices supplied by or on behalf of the Sponsor for use in the study. See Section 6.1.1 for the list of medical devices supplied by or on behalf of the Sponsor.

10.6.1 Definition of Medical Device Adverse Event

Medical Device Adverse Event

- A medical device AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

10.6.2 Definition of Medical Device Serious Adverse Event

A Medical Device SAE is any SAE that:

a. **Led to death**

b. **Led to serious deterioration in the health of the participant, that either resulted in:**

- A life-threatening illness or injury. The term ‘life-threatening' in the definition of serious’ refers to an event in which the participant was at risk of death at the time of the event. It

does not refer to an event, which hypothetically might have caused death, if it were more severe.

- A permanent impairment of a body structure or a body function.
- Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c. **Led to fetal distress, fetal death or a congenital abnormality or birth defect**

d. **Is a suspected transmission of any infectious agent via a medicinal product**

10.6.3 Definition of Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.6.4 Recording and Follow-Up of Medical Device Adverse Event and/or Serious Adverse Event and Device Deficiencies

Medical Device Adverse Event, Serious Adverse Event and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild:
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The Investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB in his/her assessment.
- The Investigator **must** review and provide an assessment of causality for each AE/SAE/device deficiency and document this in the medical notes.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Medical Device AE/SAE/Device Deficiency

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed form.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.6.5 Reporting of Medical Device Serious Adverse Events

Medical Device SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE reporting can be found in the safety reporting gateway.

Medical Device Serious Adverse Event Reporting to the Sponsor via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Investigator site file.

10.7 Appendix 7: Study Intervention Administration and Procedures

10.7.1 Preparation of Study Intervention

Only designated unmasked individuals may prepare study intervention for administration.

10.7.1.1 Aflibercept 8 mg and 2 mg

Refer to Section 6.1 for details of study intervention presentation.

The study intervention will be withdrawn using aseptic technique through an 18-gauge filtered needle attached to a 1 mL syringe. The needle will be discarded after withdrawal of the vial contents and shall not be used for IVT injection. The needle shall be replaced with a sterile 30-gauge needle for the IVT injection. The plunger alignment should be double-checked for accuracy. Injections will follow the procedures described below.

10.7.1.2 Sham

The sham procedure will use a syringe without a needle. No IVT or intraocular penetration will be performed and no drug will be administered IVT.

For the sham procedure, the unmasked injector will ensure that all procedures besides the actual injection are identical to an IVT injection of study intervention and will take precaution to ensure that the participant remains masked during the procedure.

10.7.2 Injection Procedure

The sequence of steps described below is recommended. This drug administration protocol is based upon recommendations from the Euretina Expert Consensus (Grzybowski et al. 2018).

Use of Topical Antibiotic Agents

At the time of this study, the use of topical antibiotics as prophylaxis in IVT injections, both in the preparation and post-injection, varies considerably between different practices. There is no consensus on the use of topical antibiotics, the agent to be used, and the dose administered. Therefore, topical antibiotic prophylaxis is allowed in line with local practices and at the discretion of the Investigator.

10.7.2.1 Preparation

The Investigator or designee will prepare the participant for the injection. Only designated unmasked individuals may administer study intervention. Individuals involved in performing participants' assessments must remain masked to treatment assignment.

1. Apply topical anesthetic.
2. Apply povidone iodine to eyelid margins, eyelashes, and conjunctival surface.
3. Place 1 or 2 drops of 5% povidone iodine on the ocular surface at the intended injection site.
4. Use sterilized forceps and calipers (speculum) to stabilize the globe and measure the injection site.
5. Optional: Inject 0.5 mL of 2% xylocaine without epinephrine subconjunctivally at the intended injection site (the entry site of the needle for the IVT injection should be in the inferotemporal quadrant, 3.0 to 3.5 mm from the limbus in aphakic/pseudophakic participants, and 3.5 to 4.0 mm in the phakic participants).
6. Drape.
7. Apply additional drop of 5% povidone iodine to site of injection.

10.7.2.2 Study Intervention Administration

Active Drug Procedure:

1. Insert needle at marked injection point.
2. Gently inject study intervention.
3. As the needle is withdrawn, a sterile cotton tip applicator should be rolled over the entry site to minimize the risk of drug reflux. This should be held in place for a full 10 seconds.

Sham Procedure:

1. Prepare injection site as above.
2. Use syringe without needle attached.
3. Apply syringe hub to conjunctival surface, pressing gently to simulate force of actual injection.

10.7.2.3 Post-injection Procedures

1. Indirect ophthalmoscopy in the study eye only as soon as possible but not at the same time of the IVT injection, approximately between 0 to 15 minutes after injection. The exact timing is left to the discretion of the unmasked Investigator. If the indirect ophthalmoscopy cannot be performed immediately after injection, the unmasked Investigator needs to assess the visual function of the injected eye: light perception and ability to count fingers within 0 to 5 minutes after the injection.
2. Measure IOP approximately 30 to 60 minutes (±10 minutes so measure should be at least 20 minutes after IVT injection and no more than 70 minutes after IVT injection) after injection in the study eye only. The exact timing is left to the discretion of the unmasked Investigator. Additional post-injection management procedures as recommended by the guidelines are as follows:
3. Instruct the participant to self-administer 1-2 drops of a topical antibiotic to the injected eye, 3 times a day, for an additional 3 days.
4. Post-injection reperfusion of the optic nerve:
    a. Visualize the optic nerve to verify reperfusion of the central retinal artery in the immediate post-injection period.
    b. Verify IVT location of therapeutic agent when possible.
    c. Verify that the retina is attached and that there is no new intraocular hemorrhage.
5. Intraocular pressure:

    Intraocular pressure may be lowered by pharmaceutical or surgical intervention, if required. If a Tonopen is used to check pressure, a clean Tonopen condom should be placed on the tip before taking each measurement. If an Icare tonometer is used, a clean probe should be used. If applanation tonometry is used, a disposable prism should be used or, in case this is not available, the non-disposable prism should be disinfected (e.g., swabbing tip with alcohol and allowing to dry before using it to measure IOP).
    a. Monitor IOP for at least 30 minutes after each injection.
    b. Check IOP while maintaining a clean field.
    c. Monitor IOP closely until it reaches a value that will not be expected to cause damage, e.g., below 25 mm Hg.
    d. Treatment should be initiated whenever IOP is increased to the extent that the central retinal artery remains closed and the participant has no light perception for more than 1 to 2 minutes.
    e. Transient graying or obscuration of vision following injection is expected and should not be treated.
    f. Paracentesis should be used only in extreme circumstances when the degree of pressure elevation poses an imminent and irreversible threat to vision. In the rare situation when a paracentesis is warranted, IOP should be recorded both before and after the procedure. A 0.1- to 0.2-mL paracentesis may be performed at the temporal limbus using a 27- or 30-gauge needle or surgical knife, if judged to be necessary by the Investigator.

g. Record the last IOP measurement and related treatments in the source document and on the appropriate eCRF page.

10.7.2.4 Discharge

No special precautions are required before discharge of a participant who has had an uneventful recovery from IVT injection, but participants and/or caregivers should be educated to avoid rubbing the eye and to recognize the signs and symptoms of endophthalmitis, retinal detachment, or intraocular hemorrhage. These signs and symptoms include eye pain or increased discomfort, increased redness of the eye (compared to immediately after injection), blurred or decreased vision, and increased ocular sensitivity to light. Participants should be informed that some blurring of vision is common after an injection, which is often described as seeing spots floating in the eye. Floaters usually resolve after a few days or weeks. Participants who experience AEs after injection that require additional monitoring should remain in the clinic until the condition is resolved, and should be treated according to the Investigator's medical judgment.

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